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<p>(54) Title: CORTICOTROPIN RELEASING FACTOR ANTAGONISTS</p> <p>(57) Abstract</p> <p>Corticotropin-releasing factor (CRF) antagonists having formulae (I), (II) or (III) wherein the dashed lines, A, B, Y, Z, G, R₃, R₄, R₅, R₆, R₁₆ and R₁₇ are as defined in the description, and processes for preparing them. These compounds and their pharmaceutically acceptable salts are useful in the treatment of CNS and stress-related disorders.</p>			
<p style="text-align: center;"> (I) </p>			
<p style="text-align: center;"> (II) </p>			
<p style="text-align: center;"> (III) </p>			

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5 CORTICOTROPIN RELEASING FACTOR ANTAGONISTSBackground Of The Invention

This invention relates to pyridines, pyrimidines, purinones, pyrrolopyrimidinones and pyrrolopyridinones, processes for preparing them, pharmaceutical compositions containing them, and methods of using them to treat certain central nervous system 10 (CNS) and other disorders.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. The importance of CRF antagonists is set out in the literature, e.g., as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference. A recent outline of the different activities 15 possessed by CRF antagonists is found in M. J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are effective in the treatment of a wide range of stress-related illnesses, such as depression, anxiety, headache, irritable bowel syndrome, inflammatory diseases, immune suppression, 20 Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, infertility, head trauma, stroke, and stress-induced infections in humans and animals.

Summary of the Invention

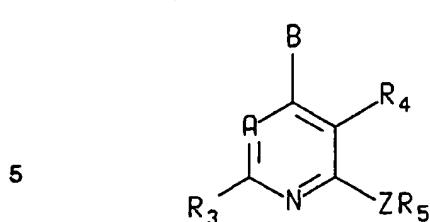
The present invention relates to a compound of the formula

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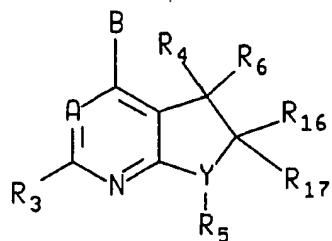
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I

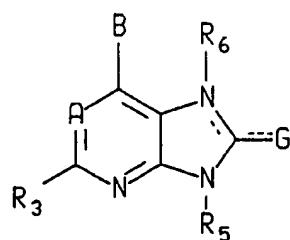


II

or

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III

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or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

25 A is -CR₁ or N;

B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁₂, -CHR₂SR₁₂, -C(S)R₂ or -C(O)R₂;

G is oxygen, sulfur, NH, NCH₃, hydrogen, methoxy, ethoxy, trifluoromethoxy, methyl, ethyl, thiomethoxy, NH₂, NHCH₃, N(CH₃)₂ or trifluoromethyl;

30 Y is -CH or N;

Z is NH, O, S, -N(C₁-C₂ alkyl) or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl;

R_1 is C_1 - C_6 alkyl which may optionally be substituted with one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3 , C_1 - C_4 alkoxy, -O-CO-(C_1 - C_4 alkyl), -O-CO-NH(C_1 - C_4 alkyl), -O-CO-N(C_1 - C_4 alkyl)(C_1 - C_2 alkyl), -NH(C_1 - C_4 alkyl), -N(C_1 - C_2 alkyl)(C_1 - C_4 alkyl), -S(C_1 - C_4 alkyl), -N(C_1 - C_4 alkyl)CO(C_1 - C_4 alkyl), -NHCO(C_1 - C_4 alkyl), -COO(C_1 - C_4 alkyl), -CONH(C_1 - C_4 alkyl), -CON(C_1 - C_4 alkyl)(C_1 - C_2 alkyl), CN, NO_2 , -SO(C_1 - C_4 alkyl) and -SO₂(C_1 - C_4 alkyl), and wherein said C_1 - C_6 alkyl and the (C_1 - C_4)alkyl moieties in the foregoing R_1 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1 - C_{12} alkyl, aryl or -(C_1 - C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C_1 - C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1 - C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by $N-R_9$ wherein R_9 is hydrogen or C_1 - C_4 alkyl; and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1 - C_4 alkyl, or with one substituent selected from bromo, iodo, C_1 - C_6 alkoxy, -O-CO-(C_1 - C_6 alkyl), -O-CO-N(C_1 - C_4 alkyl)(C_1 - C_2 alkyl), -S(C_1 - C_6 alkyl), CN, NO_2 , -SO(C_1 - C_4 alkyl), and -SO₂(C_1 - C_4 alkyl), and wherein said C_1 - C_{12} alkyl and the C_1 - C_4 alkylene moiety of said -(C_1 - C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR₁R₂ or -CR₁R₂R₁₁ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which 25 one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3 , methylthio, methylsulfonyl, CH_2OH , or CH_2OCH_3 ;

R_4 is hydrogen, C_1 - C_4 alkyl, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, trifluoromethoxy, - CH_2OCH_3 , - $CH_2OCH_2CH_3$, - $CH_2CH_2OCH_3$, - CH_2OF , CF_3 , amino, nitro, 30 -NH(C_1 - C_4 alkyl), -N(CH_3)₂, -NHCOCH₃, -NHCONHCH₃, -SO_n(C_1 - C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C_1 - C_4 alkyl), -CHO, cyano or -COO(C_1 - C_4 alkyl) wherein said C_1 - C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C_1 -

C_2 alkyl), $-N(C_1\text{-}C_2$ alkyl) $_2$, $-COO(C_1\text{-}C_4$ alkyl), $-CO(C_1\text{-}C_4$ alkyl), $C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above

5 groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, $C_1\text{-}C_6$ alkyl, and $C_1\text{-}C_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(C_1\text{-}C_6$ alkyl) $O(C_1\text{-}C_6$ alkyl), $-NHCH_3$, $-N(CH_3)_2$, $-COOH$, $-COO(C_1\text{-}C_4$ alkyl), $-CO(C_1\text{-}C_4$ alkyl), $-SO_2NH(C_1\text{-}C_4$ alkyl), $-SO_2N(C_1\text{-}C_4$ alkyl) $(C_1\text{-}C_2$ alkyl), $-SO_2NH_2$, $-NHSO_2(C_1\text{-}C_4$ alkyl), $-S(C_1\text{-}C_6$ alkyl)

10 and $-SO_2(C_1\text{-}C_6$ alkyl), and wherein the $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen or $C_1\text{-}C_6$ alkyl, wherein said $C_1\text{-}C_6$ alkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

15 R_7 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, $-O(C_1\text{-}C_4$ alkyl), $-C(O)(C_1\text{-}C_4$ alkyl), $-C(O)O(C_1\text{-}C_4$ alkyl), $-OCF_3$, CF_3 , $-CH_2OH$, $-CH_2OCH_3$ or $-CH_2OCH_2CH_3$;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

R_{12} is hydrogen or $C_1\text{-}C_4$ alkyl; and

20 R_{16} and R_{17} are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that R_{16} and R_{17} are not both methoxy or ethoxy; or R_{16} and R_{17} together form an oxo ($=O$) group;

25 with the proviso that when G is oxygen, sulfur, NH or NCH_3 , it is double bonded to the five membered ring of structure III, and with the further proviso that R_6 is absent when the nitrogen to which it is attached is double bonded to an adjacent ring carbon atom.

More specific embodiments of this invention include compounds of the formula I, II or III wherein: (a) B is $-NR_1R_2$, $-NHCHR_1R_2$, $-SCHR_1R_2$ or $-OCHR_1R_2$; R_1 is $C_1\text{-}C_6$ alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3 , or $C_1\text{-}C_2$ alkoxy group and may optionally contain one double or triple bond; and R_2 is benzyl or $C_1\text{-}C_6$ alkyl which may optionally contain one carbon-carbon double or triple bond, wherein said $C_1\text{-}C_6$ alkyl or the phenyl moiety of said benzyl may optionally be substituted with fluoro, CF_3 , $C_1\text{-}C_2$ alkyl, or $C_1\text{-}C_2$ alkoxy; or (b) B is $-CR_1R_2R_{11}$ wherein R_1 is $C_1\text{-}C_6$ alkyl

which may optionally be substituted with one C₁-C₂ alkoxy, CF₃, fluoro or hydroxy group; R₂ is benzyl or C₁-C₆ alkyl wherein said C₁-C₆ alkyl or the phenyl moiety of said benzyl may optionally be substituted with one C₁-C₂ alkyl, CF₃, C₁-C₂ alkoxy, fluoro, chloro or bromo group; and R₁₁ is hydrogen or fluoro.

5 Other more specific embodiments of this invention include compounds of the formula I, II or III wherein R₁ is C₁-C₆ alkyl which may optionally be substituted by fluoro, CF₃, hydroxy, C₁-C₂ alkyl or C₁-C₂ alkoxy and may optionally contain one carbon-carbon double or triple bond, and R₂ is C₁-C₄ alkyl which may optionally be substituted with fluoro, chloro, CF₃, C₁-C₄ alkyl or C₁-C₄ alkoxy.

10 Other more specific embodiments of this invention include compounds of the formula I, II or III wherein R₃ is methyl, chloro, or methoxy, R₄ is methyl, -CH₂OH, cyano, trifluoromethoxy, methoxy, trifluoromethyl, chloro, -COOCH₃, -CH₂OCH₃, -CH₂Cl, -CH₂F, amino or nitro; R₆ is hydrogen, methyl or ethyl and R₅ is phenyl or pyridyl wherein said phenyl or pyridyl is substituted by two or three substituents independently selected from fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, trifluoromethyl, C₁-C₆ alkyl which may optionally be substituted with one hydroxy, C₁-C₂ alkoxy or fluoro group and may optionally contain one carbon-carbon double or triple bond, -(C₁-C₄ alkylene)O(C₁-C₂ alkyl), C₁-C₃ hydroxyalkyl, hydroxy, formyl, -COO(C₁-C₂ alkyl), -(C₁-C₂ alkylene)amino, and -(C(O)(C₁-C₄ alkyl)).

15 20 Examples of preferred compounds of this invention are:

4-(1-ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine;
2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
3-ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
2-(2,6-dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
25 4-(1-ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine;
2-(4-ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
30 [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine;
[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl](1-ethyl-propyl)-amine;
butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine;
butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic
acid methyl ester;

5 [3,6-dimethyl-[2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-propyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-
methanol;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine;
1-(ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;

10 N4-(1-ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-
diamine;
N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-
amine;

15 N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine;
[3-chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)pyridin-4-yl]-[1-ethyl-propyl]-
amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-[1-ethyl-propyl]-amine;
1-(ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-
20 amine;
(1-ethyl-propyl)-[3-methoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-
yI]-amine;
(N-(1-ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-
diamine;

25 [2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-
d]pyrimidin-4-yl]-ethyl-amine;
4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-
30 d]pyrimidin-6-one;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
N-butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

5 N4-(1-ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

N4-(1-ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine;

10 [4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;

and

6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one.

The invention also relates to a pharmaceutical composition for the treatment of
15 (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced
20 by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV)
25 infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; stress-induced psychotic episodes;
30 euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune

dysfunctions (e.g., porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia;

5 amyotrophic lateral sclerosis; and hypoglycemia in a mammal, including a human, comprising an amount of a compound of the formula I, II or III, or a pharmaceutically acceptable salt thereof, that is effective in the treatment of such disorder, and a pharmaceutically acceptable carrier.

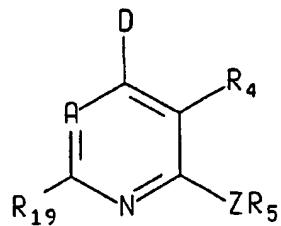
The invention further includes a method for the treatment of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitator by CRF, or (b) a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; and hypoglycemia in a mammal, including a human,

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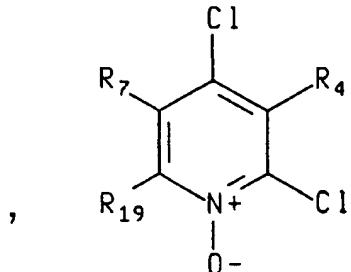
comprising administering to a subject in need of said treatment an amount of a compound of the formula I, II or III or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder.

The Invention further includes intermediate compounds of formula

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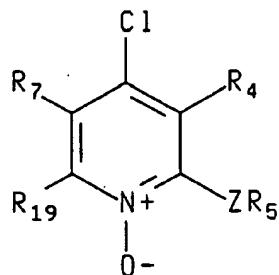
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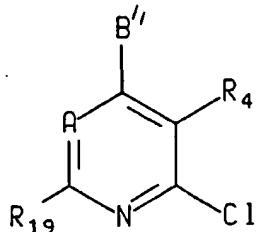
wherein R₄ and R₇ are defined as they are for formula I above; D is chloro, hydroxy or cyano; R₁₉ is methyl or ethyl; R₆ is phenyl or pyridyl and R₅ is substituted by two or three substituents independently selected from C₁-C₄ alkyl, chloro and bromo, except that no more than one such substituent can be bromo; A is N, CH or CCH₃; and Z is O, NH, N(CH₃), S or CH₂, with the proviso that when A is CH or CCH₃, then Z must be O or S.

-10-

More specific embodiments of this invention relate to compounds of the formula X or XI wherein R₇ is hydrogen or methyl.

This invention further include intermediate compounds of formula

5



10

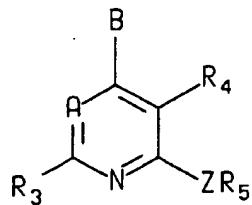
XII

wherein R₁₉ is methyl or ethyl; A is N, CH or CCH₃; and wherein when A is N, then B'' and R₄ are defined, respectively, as B and R₄ are defined for formula I, and when A is CH or CH₃, then B'' is -NR₁R₂, -NHR₁R₂, -OCHR₁R₂ or cyano and R₄ is an electron deficient group such as NO₂, -COO(C₁-C₄ alkyl), -C(=O)CH₃, -COOH or CN.

A more specific embodiment of this invention relates to compounds of the formula XII wherein B'' is -NR₁R₂ or -NHCHR₁R₂ and A is CH or CH₃.

20 This invention also relates to a process for preparing a compound of the formula I,

25



I

30 or a pharmaceutically acceptable salt thereof, wherein

A is -CR₇ or N;

B is -NR₁R₂, -NHCHR₁R₂, -OCHR₁R₂ or -SCHR₁R₂;

Z is NH, O, S, -N(C₁-C₂ alkyl) or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl;

R₁ is C₁-C₆ alkyl which may optionally be substituted with one or two substituents R₈ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF₃ and C₁-C₄ alkoxy, and wherein said C₁-C₆ alkyl and the (C₁-C₄)alkyl moiety of said C₁-C₄ alkoxy may optionally contain one carbon-carbon double or triple bond;

R₂ is C₁-C₁₂ alkyl, aryl or -(C₁-C₄ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C₁-C₆ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C₁-C₆ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R₉ wherein R₉ is hydrogen or C₁-C₄ alkyl; and wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C₁-C₄ alkyl, or with one substituent selected from bromo, iodo, C₁-C₆ alkoxy, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), CN, NO₂, -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), and wherein said C₁-C₁₂ alkyl and the C₁-C₄ alkylene moiety of said -(C₁-C₄ alkylene)aryl may optionally contain one carbon-carbon double or triple bond; or -NR₁R₂ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R₃ is methyl or ethyl;

R₄ is hydrogen, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, trifluoromethoxy, -CH₂OCH₃, -CH₂OCH₂CH₃, -CH₂CH₂OCH₃, -CH₂OF₃, CF₃, amino, nitro, -NH(C₁-C₄ alkyl), -N(CH₃)₂, -NHCOCH₃, -NHCONHCH₃, -SO_n(C₁-C₄ alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C₁-C₄ alkyl), -CHO, cyano or -COO(C₁-C₄ alkyl) wherein said C₁-C₄ alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C₁-

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C_2 alkyl), $-N(C_1-C_2$ alkyl)₂, $-COO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

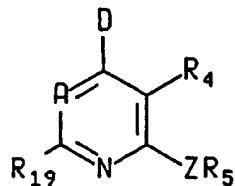
R_6 is phenyl or pyridyl, and R_6 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(C_1-C_6$ alkyl) $O(C_1-C_6)$ alkyl, $-NHCH_3$, $-N(CH_3)_2$, $-COOH$, $-COO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-SO_2NH(C_1-C_4$ alkyl), $-SO_2N(C_1-C_4$ alkyl) $(C_1-C_2$ alkyl), $-SO_2NH_2$, $-NHSO_2(C_1-C_4$ alkyl), $-S(C_1-C_6$ alkyl) and $-SO_2(C_1-C_6$ alkyl), and wherein the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_6 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl; and

R_7 is hydrogen or methyl;

or a pharmaceutically acceptable salt of such compound;

comprising reacting a compound of the formula

15



20

IV

wherein R_{19} is methyl or ethyl, D is chloro and A, Z, R₄ and R₅ are defined as above, with a compound of the formula BH, wherein B is defined as above, in the presence of a base; and then optionally converting the compound of formula I formed 25 in such reaction into a pharmaceutically acceptable salt.

This invention also relates to a process for preparing a compound of the formula

30



I

or a pharmaceutically acceptable salt thereof, wherein

10 A is -CR, or N;
 B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂,
 -CHR₂OR₁₂, -CHR₂SR₁₂, -C(S)R₂ or -C(O)R₂;
 Z is NH, O, S, -N(C₁-C₂ alkyl) or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and
 15 the other is hydrogen or methyl;
 R₁ is C₁-C₆ alkyl which may optionally be substituted with one or two substituents R₈ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF₃ and C₁-C₄ alkoxy, and wherein said C₁-C₆ alkyl and the (C₁-C₄)alkyl moiety of said C₁-C₄ alkoxy may optionally contain one carbon-carbon double
 20 or triple bond;
 R₂ is C₁-C₁₂ alkyl, aryl or -(C₁-C₄ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C₁-C₆ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at
 25 least 4 ring members and the cycloalkyl moiety of said -(C₁-C₆ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R₉ wherein R₉ is hydrogen or C₁-C₄ alkyl; and wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents
 30 independently selected from chloro, fluoro and C₁-C₄ alkyl, or with one substituent selected from bromo, iodo, C₁-C₆ alkoxy, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), CN, NO₂, -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), and wherein

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said C_1 - C_{12} alkyl and the C_1 - C_4 alkylene moiety of said $-(C_1$ - C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or $-NR_1R_2$ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of

5 the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3 , methylthio, methylsulfonyl, CH_2OH , or CH_2OCH_3 ;

R_4 is hydrogen, C_1 - C_4 alkyl, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2OF$, CF_3 , amino, nitro,

10 $-NH(C_1$ - C_4 alkyl), $-N(CH_3)_2$, $-NHCOCH_3$, $-NHCONHCH_3$, $-SO_n(C_1$ - C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, $-CO(C_1$ - C_4 alkyl), $-CHO$, cyano or $-COO(C_1$ - C_4 alkyl) wherein said C_1 - C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, $-NHCOCH_3$, $-NH(C_1$ - C_2 alkyl), $-N(C_1$ - C_2 alkyl)₂, $-COO(C_1$ - C_4 alkyl), $-CO(C_1$ - C_4 alkyl), C_1 - C_3 alkoxy, C_1 - C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl or pyridyl and R_6 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(C_1$ - C_6 alkyl) $O(C_1$ - C_6 alkyl), $-NHCH_3$, $-N(CH_3)_2$, $-COOH$, $-COO(C_1$ - C_4 alkyl),

20 $-CO(C_1$ - C_4 alkyl), $-SO_2NH(C_1$ - C_4 alkyl), $-SO_2N(C_1$ - C_4 alkyl) $(C_1$ - C_2 alkyl), $-SO_2NH_2$, $-NHSO_2(C_1$ - C_4 alkyl), $-S(C_1$ - C_6 alkyl) and $-SO_2(C_1$ - C_6 alkyl), and wherein the C_1 - C_4 alkyl and C_1 - C_6 alkyl moieties of the foregoing R_6 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl; and

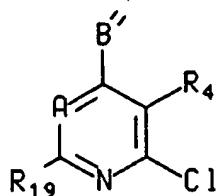
25 R_7 is hydrogen or methyl;

with the proviso that when A is CH or CCH_3 , then R_4 is an electron deficient group such as NO_2 , $-COO(C_1$ - C_4 alkyl), $-C(=O)CH_3$, $-COOH$ or CN ;

or a pharmaceutically acceptable salt of such compound;

comprising reacting a compound of the formula

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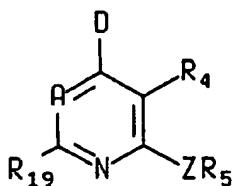


III

wherein R_{19} is methyl or ethyl and A is N, CH or CCH_3 ; and wherein when A is N, then B'' and R_4 are defined, respectively, as B and R_4 are defined in claim 1, and when A is CH or CH_3 , then B'' is $-NR_1R_2$, $-NHR_1R_2$, $-OCHR_1R_2$ or cyano and R_4 is an electron deficient group such as NO_2 , $-COO(C_1-C_4\text{ alkyl})$, $-C(=O)CH_3$, $-COOH$ or CN;

10 with a compound of the formula R_5ZH , wherein R_5 and Z are defined as above, and then optionally converting the compound of formula I formed by such reaction into a pharmaceutically acceptable salt.

15 This invention also relates to a process for preparing a compound of the formula



IV

a wherein R_{19} is methyl or ethyl;

D is chloro;

25 A is $-CR_7$ or N;

Z is NH, O, S, $-N(C_1-C_2\text{ alkyl})$ or $-C(R_{13}R_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

30 R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2OF_3$, CF_3 , amino, nitro, $-NH(C_1-C_4\text{ alkyl})$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHCONHCH_3$, $-SO_n(C_1-C_4\text{ alkyl})$ wherein n is 0, 1 or 2, cyano, hydroxy, $-CO(C_1-C_4\text{ alkyl})$, $-CHO$, cyano or $-COO(C_1-C_4\text{ alkyl})$ wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and may optionally

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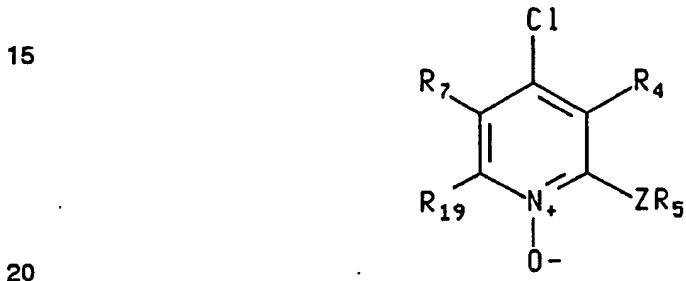
be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), C₁-C₃ alkoxy, C₁-C₃ thioalkyl, fluoro, chloro, cyano and nitro; and

R₅ is phenyl or pyridyl, and R₅ is substituted with from one to three substituents

5 independently selected from fluoro, chloro, C₁-C₈ alkyl, and C₁-C₈ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, -(C₁-C₈ alkyl)O(C₁-C₈ alkyl), -NHCH₃, -N(CH₃)₂, -COOH, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -S(C₁-C₆ alkyl) and -SO₂(C₁-C₆ alkyl), and wherein the C₁-C₄ alkyl

10 and C₁-C₈ alkyl moieties of the foregoing R₅ groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

comprising reacting a compound of the formula



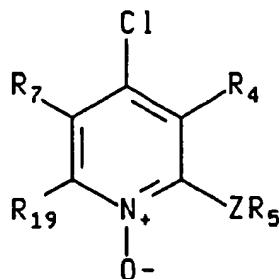
X

wherein R₁₉, R₄ and R₅ are defined as above and R₁₉ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₄ alkyl), -C(O)(C₁-C₄ alkyl), -C(O)O(C₁-C₄ alkyl), -OCF₃, CF₃, -CH₂OH, -CH₂OCH₃ or -CH₂OCH₂CH₃, with phosphorus trichloride.

25 This invention also relates to a process for preparing a compound of the formula

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5



X

10 wherein R₁₉ is methyl or ethyl;A is -CR₇ or N;

Z is O, S, or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl;

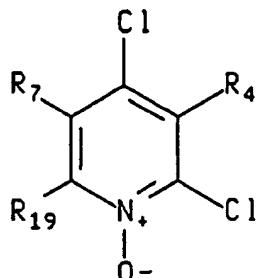
15 R₄ is hydrogen, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, trifluoromethoxy, -CH₂OCH₃, -CH₂OCH₂CH₃, -CH₂CH₂OCH₃, -CH₂OF₃, CF₃, amino, nitro, -NH(C₁-C₄ alkyl), -N(CH₃)₂, -NHCOCH₃, -NHCONHCH₃, -SO_n(C₁-C₄ alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C₁-C₄ alkyl), -CHO, cyano or -COO(C₁-C₄ alkyl) wherein said C₁-C₄ alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), C₁-C₃ alkoxy, C₁-C₃ thioalkyl, fluoro, chloro, cyano and nitro; and

20 R₆ is phenyl or pyridyl, and R₅ is substituted with from one to three substituents independently selected from fluoro, chloro, C₁-C₆ alkyl, and C₁-C₆ alkoxy, or with one 25 substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, -(C₁-C₆ alkyl)O(C₁-C₆ alkyl), -NHCH₃, -N(CH₃)₂, -COOH, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -S(C₁-C₆ alkyl) and -SO₂(C₁-C₆ alkyl), and wherein the C₁-C₄ alkyl and C₁-C₆ alkyl moieties of the foregoing R₅ groups may optionally be substituted with 30 one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

comprising reacting a compound of the formula

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5



XI

10 wherein R₄, R₇ and R₁₉ are defined as above, with a compound of the formula R₅OH or R₅SH, wherein R₅ is defined as above, in the presence of a base.

Detailed Description of the Invention

Methods of preparing the compounds and compositions of this invention are described below. In the discussion and reaction schemes that follow, R₁ through R₉, R₁₁, R₁₂, R₁₆, R₁₇, R₁₈, A, B, G, the dashed lines and structural formulae I, II, III, X, XI, XII and IV, unless otherwise indicated, are defined as above.

Whenever reference is made herein to C₁-C₆ alkyl, a straight or branched chain alkyl of one to six carbon atoms is meant, such as methyl, ethyl, isopropyl, t-butyl or hexyl.

20 Whenever R₂ or R₅ is a heterocyclic group, attachment of the group is through a carbon atom.

Whenever reference is made herein to C₁-C₄ alkyl or C₁-C₆ alkyl which "may contain one double or triple bond" in the definitions of R₁, R₂ and R₃, it is understood that at least two carbons are present in the alkyl for one double or triple bond.

25 Whenever reference is made herein to halo or halogen, fluoro, chloro, bromo or iodo is meant unless indicated otherwise.

Compounds of the formula I wherein B is -NR₁R₂, -NHCHR₁R₂, -OCHR₁R₂ or -SCHR₁R₂, and R₃ is methyl, ethyl or chloro (hereinafter R₁₉) may be prepared by reaction of a compound of the formula IV wherein D is Cl, and A, R₄, R₆, and Z are as defined above with reference to formula I, with a compound of the formula BH wherein B is as defined immediately above. The reaction is carried out in a solvent in the presence of a base at a temperature of between about 0° to about 230°C. Suitable solvents are organic solvents such as tetrahydrofuran (THF), acetonitrile,

dimethylsulfoxide (DMSO), acetone, C_2 - C_{15} alkyl alcohol, chloroform ($CHCl_3$), benzene, xylene, toluene, sulfolane, pyridine, quinoline, 2,4,6-trimethylpyridine, acetamide, di-(C_1 - C_2)alkylacetamide or 1-methyl-2-pyrrolidinone.

A preferred method of preparing compounds of the formula I wherein A is -CR,
5 and B is -NR₁R₂ or -NHCHR₁R₂ is the two step procedure described below. First, a compound of the formula IV is reacted with an excess of R₁NH₂ or NH₃ or an equivalent NH₃ precursor (e.g., NaN₃, nBu₄N⁺N₃⁻ or NH₂OH) at temperature from about 75°C to about 250°C and at a pressure from about 0 to about 300 psi, in an appropriate solvent, as described above, to form a compound of the formula I wherein B is -NHR₁,
10 -NH₂, -NH₂OH or -N₃. Compounds of the formula I wherein B is -N₃ or -NH₂OH can be converted into the corresponding compounds of formula I wherein B is -NH₂ by methods well known in the art such as hydrogenation or reduction. Alkylation of a compound of the formula I wherein B is -NHR₁ or -NH₂ with an appropriate alkyl halide in the presence of an appropriate base such as lithium or sodium bistrimethylsilylamine,
15 lithium or sodium diisopropylamide, n-butyllithium or potassium t-butoxide, in an appropriate solvent such as THF, dioxane or methylene chloride, will yield the corresponding compound of formula I wherein B is -NR₁R₂. Alternatively, reductive amination of a compound of the formula I wherein B is -NHR₁ or -NH₂, for example, acylation, followed by reduction with a borohydride (e.g., sodium borohydride) will form
20 the corresponding compound of formula I wherein B is -NR₁R₂ or NHCHR₁R₂.

When B is -NR₁R₂ or -NHCHR₁R₂, an excess of BH may be used both as a reagent and as a base. Bases other than BH such as potassium carbonate, tri-(C_1 - C_8)alkylamine or sodium hydride may also be used. The reaction is carried out at a temperature of about 75° to 230°C. When the reaction is carried out in the presence
25 of a base, such as sodium hydride, potassium C₁-C₄ alkoxide, or an organolithium compound such as n-butyllithium, a molar equivalent of the amine is used.

When B is -OCHR₁R₂ or -SCHR₁R₂, a base which is capable of deprotonating BH may be used, such as an alkali metal hydride such as sodium or potassium hydride, or an organometallic base such as sodium diisopropylamide, sodium bis(trimethylsilyl)amide, lithiumdiisopropylamide, lithium bis(trimethylsilyl)amide, sodium or potassium C₁-C₄ alkoxide, or n-butyllithium. The solvent used can be, for example, tetrahydrofuran, acetonitrile, dimethylsulfoxide, acetone, methylene chloride, toluene, a C₂-C₅ alcohol, chloroform, benzene, xylene, or 1-methyl-2-pyrrolidinone, and the

reaction temperature can range from about 0°C to about 180°C, and is preferably from about 50°C to about 80°C.

Compounds of the formulae I, II and III wherein B is as defined with reference to formulae I, II and III and R₃ is defined with reference to the same except that R₃ is

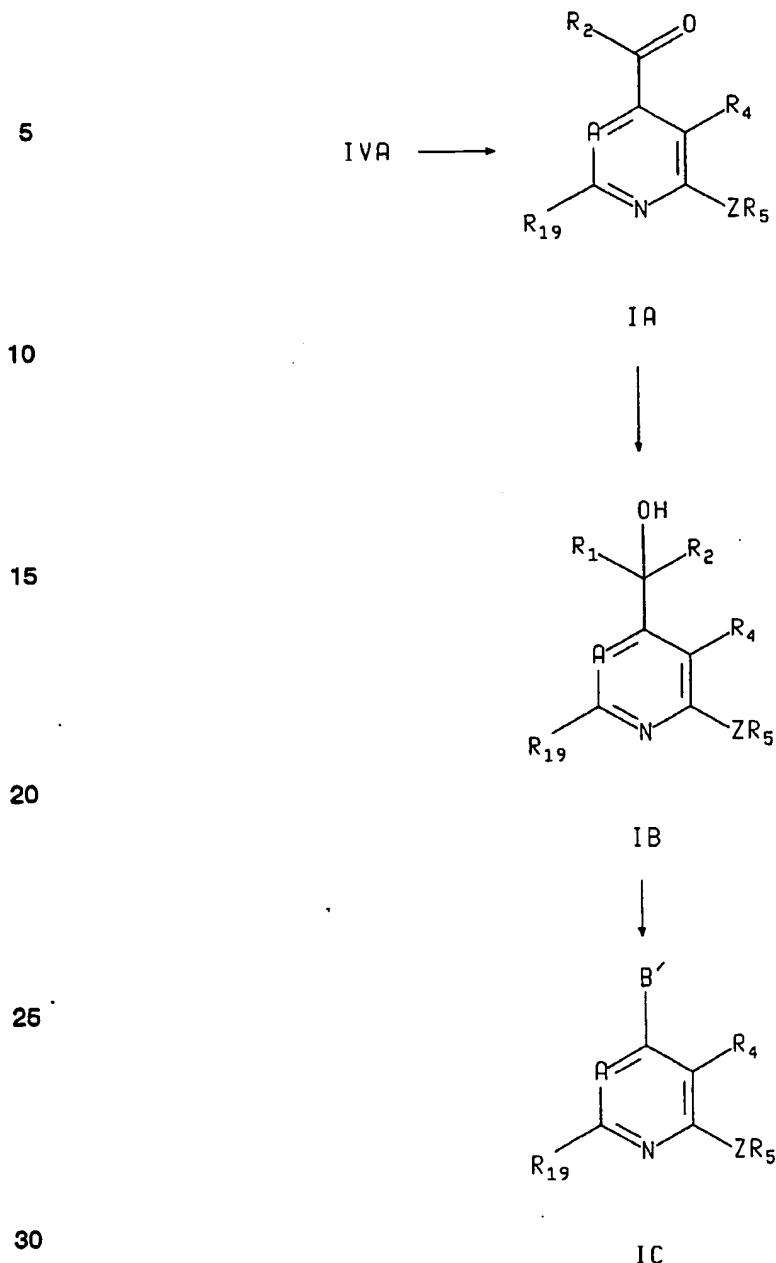
- 5 not methyl or ethyl (hereinafter R₂₀, which is defined as R₃ with the exception that it can not be methyl or ethyl) may be prepared by reacting a compound of the formulae I, II or III wherein R₃ is chloro with a nucleophile of the formula R₂₀H with or without an organic or inorganic base. Suitable bases include sodium and sodium hydride, when R₂₀H is an alkanol or an alkane thiol; and weaker bases such as potassium carbonate
- 10 or triethylamine when R₂₀H is an amine. The compounds of formula I wherein R₂₀ is fluoro may be prepared from the corresponding compounds wherein R₂₀ is chloro on reaction with tetrabutylammonium fluoride. Suitable solvents are dimethylsulfoxide, tetrahydrofuran, or methylene chloride, preferably tetrahydrofuran.

Compounds of the formula I wherein B is -CR₁R₂R₁₁, -C(C=CR₂R₁₂)R₁,

- 15 -CHR₂OR₁₂, -CHR₂SR₁₂, or -C(O)R₂, and R₃ is R₁₉, as defined above, may be prepared as depicted in Scheme I.

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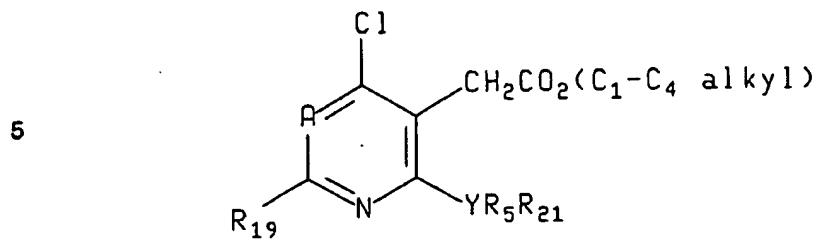
SCHEME 1



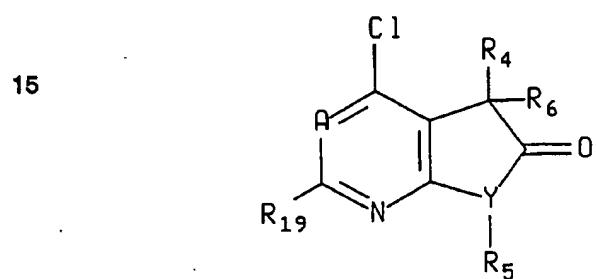
Compounds of the formula IV wherein D is cyano and A, R₄, R₅, and R₁₉ are as defined above having formula IVA (not shown), prepared by reacting the corresponding compound wherein D is chloro with potassium cyanide or copper cyanide in dimethylsulfoxide, 1-methyl-2-pyrrolidinone, N,N-dimethylformamide (DMF) or 5 acetamide, are reacted with a Grignard reagent containing group R₂, as defined above, to form the compounds of formula IA. Further reaction of the compound of formula IA with a Grignard reagent containing R₁ as defined above provides the compound of formula IB. Corresponding compounds of formula IC wherein B' is -CR₁R₂R₁₁, or 10 -C(C=CR₂R₁₂)R₁ may be prepared by conventional methods. Thus, reaction of IB with an acid, such as concentrated sulfuric acid in acetic acid, or Burgess inner salt, such as (carboxysulfamoyl)triethylammonium hydroxide methyl ester, gives a compound of formula IC wherein B' is -C(=CR₂R₁₂)R₁. Hydrogenation of a compound wherein B' is 15 -C(=CR₂R₁₂)R₁ using a palladium/carbon (Pd/C) or platinum dioxide catalyst gives a compound IC wherein B' is CHR₂R₂. Reaction of compound IB with diethylaminosulfur trifluoride or triphenylphosphine/carbontetrachloride affords a compound IC wherein B' is -CR₁R₂F or -CR₁R₂Cl, respectively. Reduction of a compound of formula IA with sodium borohydride gives a compound I wherein B is -CHR₂OH. Alkylation of this 20 -CHR₂OH group with alkyl halide such as alkyl iodide in the presence of a base such as sodium hydride at room temperature affords a compound of formula I wherein B is -CHR₂OR₁₂.

Compounds of the formula II wherein R₃ is R₁₉ as defined above may be prepared from compounds of the formula IV wherein R₁₉, R₄, R₅ and A are as defined before, D is chloro, and YR₂₁ is NH or -CHR₂₁ wherein R₂₁ is cyano or -COO(C₁-C₄ alkyl), hereafter formula IVB, as shown in Scheme 2.

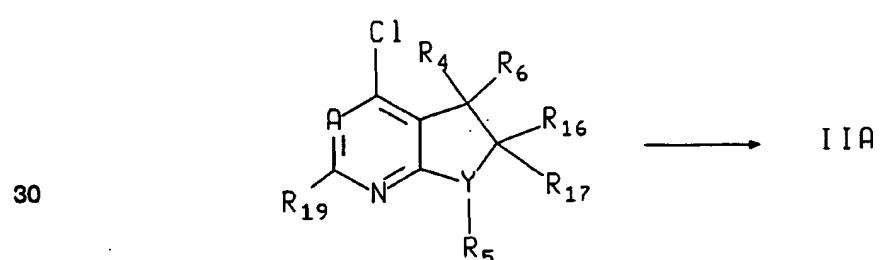
SCHEME 2



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vii



VIII

Compounds of the formula VII wherein R₄ and R₆ are each hydrogen and Y is N may be prepared by heating compounds of formula IVB with an acid catalyst in a suitable solvent such as toluene, benzene, t-butanol, acetonitrile and acetone, preferably toluene. The acid catalyst may be sulfuric acid, hydrochloric acid, p-toluene sulfonic acid, or methylsulfonic acid, preferably p-toluene sulfonic acid.

When Y in formula IVB is CH or N, a base may be used to deprotonate the proton of the compound of formula IVB. Suitable solvents are tetrahydrofuran, toluene, and methylene chloride, suitable reaction temperatures are between about -78°C and 100°C, preferably -78° to 50°C, and suitable bases are sodium hydride, potassium hydride, potassium t-butoxide, lithium bis(trimethylsilyl) amide, and lithium or sodium diisopropylamide.

Compounds of the formula VII wherein R₄ and R₆ are each hydrogen may be deprotonated with a base such as sodium hydride, or an organometallic compound such as lithium bis(trimethylsilyl)amide followed by quenching with an electrophile compound containing the group R₄, such as R₄L wherein L is a leaving group such as iodo, bromo, mesylate, tosylate or with p-tolyl-N-fluoro-N-C₁-C₆ alkyl sulfonamide, iodine, p-nitrobenzene, dimethylformamide, di(C₁-C₄ alkyl)ketone, formaldehyde, (C₁-C₄ alkyl) aldehyde or bromine, to provide a compound of formula VII wherein R₄ is fluoro, chloro, bromo, iodo, hydroxy, C₁-C₄ alkyl, S(C₁-C₄ alkyl), CHO, CH(OH)(C₁-C₄ alkyl), C(OH)(di-C₁-C₄ alkyl) or CH₂OH. Further conventional alkylation of the hydroxy group or oxidation of the thioalkyl group leads to compounds of formula VII wherein R₄ is C₁-C₄ alkoxy and SO_n(C₁-C₄ alkyl) wherein n is 1 or 2, respectively. Oxidation of compounds of formula VII wherein R₄ is hydroxy and R₆ is hydrogen affords corresponding compounds wherein CR₄R₆ is C=O, which on reductive amination with an appropriate amine convert into corresponding compounds wherein R₄ is amino. The compounds of formula VII wherein R₄ is nitro or amino may be formed by reacting compounds of formula VII wherein R₄ and R₆ are both hydrogen with alkyl nitrite to form compounds wherein CR₄R₆ is C=NOH and oxidizing or reducing to give the compounds of formula VII wherein R₄ is nitro or amine, respectively.

Compounds of the formula VII, when one of R₄ and R₆ is hydrogen, may be converted into corresponding compounds wherein R₁₆ and R₁₇ are both hydrogen by reduction with a reducing agent such as lithium aluminum hydride in tetrahydrofuran. The same reduction leads to compounds wherein R₁₆ is hydrogen and R₁₇ is hydroxy,

when both of R_4 and R_6 are not hydrogen. Alkylation of R_{17} is hydroxy with C_1 - C_4 alkyl iodide in the presence of sodium hydride gives the corresponding compound wherein R_{17} is $O(C_1$ - C_4 alkyl). Reaction of compounds of formula VII with an organometallic compound such as $d(C_1$ - C_6 alkyl)zinc, C_1 - C_6 alkyl lithium, or C_1 - C_6 alkyl magnesiumbromide affords compounds of formula VIII wherein one of R_{16} or R_{17} is C_1 - C_6 alkyl and the other is hydroxy.

5 The conversion of compounds of formula VIII to corresponding compounds of formula IIA is by the methods described above for preparation of compounds of formula I.

10 The compounds of formula III wherein G is oxygen or sulfur and R_6 is hydrogen may be prepared by reacting compounds of formula I wherein R_4 is amino and Z is NH with phosgene, diphosgene, triphosgene or thiophosgene. The reaction is in the presence of a base such as tri(C_1 - C_4 alkyl)amine in a suitable solvent, preferable tetrahydrofuran at about $-78^\circ C$ to about $50^\circ C$, preferably at $0^\circ C$ to room temperature.

15 Standard alkylation of these compounds wherein R_6 is hydrogen with a suitable base such as sodium hydride in a suitable solvent such as dry tetrahydrofuran provides compounds of the formula III wherein R_6 is C_1 - C_4 alkyl.

Compounds of the formula III wherein G is alkyl may be prepared by reacting a compound of the formula I wherein R_4 is amino and Z is NH with a compound of the

20 formula $GC(OC_1$ - C_2 alkyl)₃ in the presence of an acid such as p-toluenesulfonic acid (p-TsOH), methanesulfonic acid (MsOH), hydrogen chloride gas (HCl_g) or concentrated sulfuric acid (H₂SO₄) in an appropriate solvent such as toluene, xylene, benzene, dioxane or THF at a temperature from about room temperature to about $140^\circ C$, preferably from about $50^\circ C$ to about the reflux temperature. Alternatively, a compound

25 of the formula I wherein R_4 is amino and Z is NH can be reacted with $[G(C=O)]_2O$, $G(C=O)Cl$ or $G(C=O)F$ in the presence of a base such as pyridine, a derivative of pyridine or a tri(C_1 - C_4 alkyl)amine, in an appropriate solvent such as CH₂Cl₂, CHCl₃, THF, dioxane, toluene or benzene, at a temperature from about $0^\circ C$ to about the reflux temperature of the reaction mixture, preferably from about $0^\circ C$ to about room

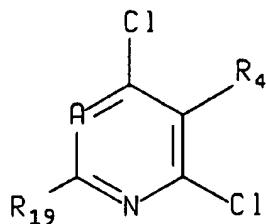
30 temperature, followed by ring cyclization under acidic conditions (e.g., with pTSOH, MSOH, HCl_g, hydrogen bromide gas (HBr_g) or concentrated H₂SO₄). The ring cyclization can be carried out in an appropriate solvent such as a C_1 - C_6 alcohol, toluene, xylene, benzene, dioxane or THF. Suitable temperatures for this reaction can

range from about room temperature to about 140°C. Preferably, the reaction temperature is between about 50°C and about the reflux temperature.

Compounds of the formula III wherein G is -O-(C₁-C₂ alkyl) or -OCF₃ may be prepared by reacting a compound of the formula III wherein G is oxygen and R₆ is hydrogen with a compound of the formula GOSO₂CF₃ in the presence of a base such as tri(C₁-C₄ alkyl)amine, or with lithium bis(trimethylsilyl)amide in HMPA or DMF, and then quenching the reaction with a compound of the formula GOSO₂OG or G-X wherein X is bromo, chloro or SO₃CF₃.

The compounds of formula IV wherein D is chloro and ZR₅ is NHR₅ may be prepared from compounds of formula V:

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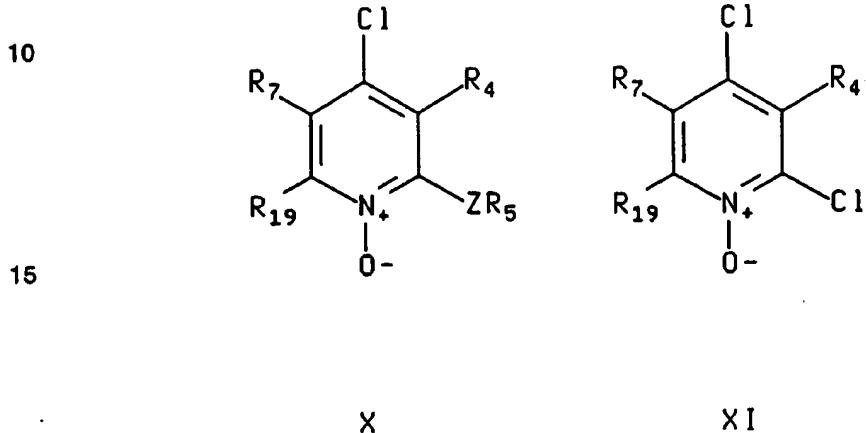


V

wherein A and R₄ are as defined with reference to formula I and R₁₉ is as defined above, by reaction with R₅NH₂. The reaction is in tetrahydrofuran or dimethylsulfoxide at about 0°C to about 150°C, preferably 50° to 130°C. The compounds of formula IV wherein D is chloro and Z is O, S, CHR₂₁ wherein R₂₁ is an electron deficient group such as cyano, C(=O)R, COOR, wherein R is C₁-C₄ alkyl, benzoyl or allyl, or SO_n-phenyl wherein n = 0, 1 or 2 may be prepared by reacting compounds of formula V with R₅OH, R₅SH, R₅NH₂ or R₅CHR₂₁. The reaction proceeds in the presence of a base which is capable of deprotonating R₅ZH, such as sodium hydride, potassium hydride, potassium carbonate, lithium or sodium bis(trimethylsilyl)amide, lithium or sodium dialkylamide, sodium or potassium (C₁-C₄ alkoxide) or n-butyllithium, with or without other organometal halides such as copper (I) bromide, iodide or chloride, copper (II) oxide, copper (I) oxide, copper metal and trialkyltinchloride. Examples of solvents that may be used are tetrahydrofuran, dimethylsulfoxide, acetonitrile, methylene chloride, 1-methyl-2-pyrrolidinone, pyridine, quinoline, N,N-dialkylacetamides, 2,4,6-trimethylpyridine, N,N-dialkylformamides, e.g., N,N-dimethylformamide (DMF),

hexamethyl phosphoramide and toluene. The reaction temperature may range from about 0°C to about 180°C, and is preferably from about 0° to about 150°C.

Compounds of the formula IV wherein A is CR₇, D is chloro and Z is O, S, CHR₂₁ may be prepared by reduction of compounds of formula X, depicted below, wherein R₇ and Z are as defined immediately above, with a reducing agent such as phosphorous trichloride in an appropriate solvent such as methylene chloride or chloroform at temperature from about 0°C to about 100°C, preferably from about room temperature to about the reflux temperature of the solvent.



20 Compounds of the formula X may be prepared from compounds of the formula XI, depicted above, wherein R₄ is as defined as it is for formula I and R₁₉ is as defined above (i.e., methyl or ethyl), by reaction with a compound of the formula R₅OH, R₅SH or R₅CHR₂₁. This reaction proceeds in the presence of a base which is capable of deprotonating R₅ZH, such as sodium hydride, potassium hydride, lithium, sodium or potassium bis(trimethylsilyl)amide, lithium, sodium or potassium dialkylamide, sodium or potassium C₁-C₄alkoxide, or n-butyllithium. Suitable solvents include tetrahydrofuran, dioxane, dimethylsulfoxide, 1-methyl-2-pyrrolidinone, pyridine, N,N-di-(C₁-C₄ alkyl)acetamides, acetamide, N,N-di-(C₁-C₄ alkyl)formamides, acetonitrile, methylene chloride, toluene and xylene. Suitable reaction temperatures may range from about -25 to about 150°C, and are preferably between about -40° to about 150°C.

25 Compounds of the formula XI may be prepared by reacting the corresponding compounds of formula V wherein A is -CR₇ and R₄ and R₁₉ are defined as above, with an oxidizing agent such as m-chloroperbenzoic acid, peracetic acid or pertrifluoroacetic

acid, in a solvent such as methylene chloride, chloroform, acetic acid, DMF, methanol or a mixture of one or more of the foregoing solvents, at temperature from about 0°C to about 100°C, preferably from about room temperature to about 60°C.

When R₄ is an electron withdrawing group such as a NO₂, -COO(C₁-C₄ alkyl), -COOH, CN or -CO(C₁-C₄)alkyl, the reaction order for the coupling reactions that introduce the B and ZR₅ groups in the synthesis of compounds of formula I may be reversed. The B group may be introduced before the ZR₅ coupling step using the methods analogous to those described above. For example, compounds of the formula I wherein R₄ is an electron deficient group may be prepared by reacting a compound of the formula XII with a compound of the formula HZR₆. Compounds of the formula XII may be prepared by reacting a compound of the formula V wherein A is CR₁ and R₁₉ and R₄ are defined as above with a compound of the formula B''H in the presence of a base.

Compounds of the formula IV wherein D is chloro and Z is -N(C₁-C₄ alkyl) may be prepared by reacting the corresponding compounds wherein Z is NH with a base, at a temperature from about -78°C to about 100°C, preferably from about 0°C to about room temperature, followed by quenching with C₁-C₄ alkyl iodide or bromide. Suitable bases include, for example, sodium hydride, lithium or sodium bis(trimethylsilyl)amide, lithium or sodium dialkylamide, and n-butyllithium. Suitable solvents include, for example, tetrahydrofuran, dimethylsulfoxide, toluene, benzene or methylene chloride.

Compounds of the formula IV wherein D is chloro, hydroxy or OP wherein P is a standard protecting group for hydroxy and Z is -CR₁₃R₁₄ may be prepared by alkylation, using an R₁₃ containing alkylating agent such as R₁₃I, compounds of the formula IV wherein Z is -CHR₂₁ in the presence of a base that is capable of deprotonating the proton in the Z group, as mentioned above, followed by quenching with an R₁₄ containing alkylating agent such as R₁₄I. Heating compounds of the formula IV wherein D is chloro or hydrogen and Z is -CH(CN) in about 85% phosphoric acid at about the reflux temperature yields the corresponding compounds of formula IV wherein D is hydroxy and Z is CH₂. Deprotonation of the compounds of formula IV wherein Z is CH₂ with a base, such as described above for deprotonation of R₅ZH, followed by quenching with a suitable electrophile such as a (C₁-C₆ alkyl)iodide, iodine, bromine, acetylchloride, formaldehyde, acetone, p-tolyl-N-fluoro-N-(C₁-C₆ alkyl)sulfonamide, nitrobenzene, C₁-C₆ alkyl nitrite, ethylene oxide or dihaloethane yields

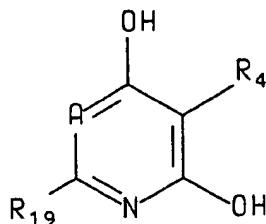
the corresponding compounds of formula IV wherein Z is -CHR₁₃, -CH(OH), cyclopropyl or -C(NOH). Further alkylation of compounds wherein Z is -CHR₁₃, e.g., as described immediately above, with an alkylating agent of the formula R₁₄I, produces the corresponding compounds wherein Z is -C(R₁₃R₁₄).

5 Conversion of -C(R₅)NOH or -CH(OH)R₅ to C(O)R₅ may be accomplished by known methods. Hydrogenation or reduction of compounds wherein Z is -C=NOH provides compounds wherein Z is -CHNH₂. Some of the intermediates may require a protecting or deprotecting procedure to control the reaction selectivity using standard organic chemistry.

10 Compounds of the formula V wherein A is N (hereinafter referred to as compounds of the formula VB) or A is CR, (i.e., compounds of the formula VA), and R₄ and R₁₉ are defined as they are for formula I, may be prepared by reacting the corresponding compounds of formulae VIB and VIA, respectively, with 1 equivalent or an excess of POCl₃ at a temperature from about room temperature to about 180°C, 15 preferably at the reflux temperature, with or without a solvent. Compounds of formula VIA may be prepared by the methods analogous to those described in the literature and well known to those skilled in the art. (See Helv. Chimica Acta., 25, p. 1306-1313 (1942)).

20 Compounds of formula VIB may be prepared by reacting 1 equivalent of the HCl salt of R₁₉C(=NH)(NH₂), 1 equivalent of R₄CH(COO-(C₁-C₂ alkyl))₂, and 2 equivalents of a base such as a sodium alkoxide, e.g., sodium methoxide in a mixture of an alcohol (e.g., methanol), and acetone at a temperature from about 50°C to about 200°C, preferably at the reflux temperature.

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VIA, A = CR₇

VIB, A = N

When compounds of this invention contain one or more chiral centers, it is understood that the invention includes the racemic mixtures as well as all individual enantiomers and diastereomers of such compounds, and mixtures thereof.

The acid addition salts of compounds of the formulae I, II and III ("the active compounds of this invention) can be prepared in a conventional manner by treating a solution or suspension of the corresponding free base with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques can be employed to isolate the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, 10 sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

The active compounds of this invention may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile 15 aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formulae I, II and III and their pharmaceutically acceptable carriers can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients 20 such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, methylcellulose, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, 25 lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active 30 ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions containing an active compound of this invention or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first 5 rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosages for compounds of the formulae I, II or III and their salts 10 will depend on the intended route of administration and factors such as the age and weight of the patient, as generally known to a physician. The dosages will also depend on the particular illness to be treated. For instance, the daily dosage for stress-induced illnesses, inflammatory disorders, Alzheimer's disease, gastro-intestinal diseases, anorexia nervosa, hemorrhagic stress and drug and alcohol withdrawal symptoms will 15 generally range from about 0.1 to about 50 mg/kg body weight of the patient to be treated.

Methods that may be used to determine the CRF antagonist activity of the active compounds of this invention and their pharmaceutically acceptable salts are described in Endocrinology, 116, 1653-1659 (1985) and Peptides, 10, 179-188 (1985). The 20 binding activities for compounds of formulae I, II and III, expressed as IC₅₀ values, generally range from about 0.5 nanomolar to about 10 micromolar.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra 25 ('H NMR) and C¹³ nuclear magnetic resonance spectra (C¹³ NMR) were measured for solutions in deuteriochloroform (CDCl₃) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

The following abbreviations are used in the Examples: Ph=phenyl; 30 iPr=isopropyl; HRMS=high resolution mass spectrum.

Example 1A. Butyl-(6-chloro-2,5-dimethyl-pyrimidin-4-yl)-ethylamine

A mixture of 2,5-dimethyl-4,6-dichloro-pyrimidine (0.999 g, 5.64 mmol) in 5ml of acetonitrile was treated with triethylamine (0.571 g, 5.65 mmol) and N-butyl-ethyl-amine (0.570 g, 5.65 mmol) and heated at reflux overnight. The mixture was cooled, diluted with water and dilute hydrogen chloride, and extracted with ethyl acetate. The organic layer was neutralized with saturated potassium carbonate, washed with brine, dried and concentrated to give 0.877 g (64%) of title compound as a yellow oil. ^1H NMR (CDCl_3) δ 0.90 (t, 3H), 1.15 (t, 3H), 1.22-1.36(m, 2H), 1.5-1.6(m, 2H), 2.20 (s, 3H), 2.45 (s, 3H), 3.25-3.48 (m, 4H) ppm.

B. N-Butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of butyl-(6-chloro-2,5-dimethyl-pyrimidin-4-yl)-ethylamine (398 mg, 1.65 mmol), 2,4,6-trimethylaniline (4.04 g, 30 mmol) and diisopropyl-ethyl-amine (200 mg, 1.55 mmol) was heated at 210 to 230°C overnight. The mixture was quenched with water and dilute hydrogen chloride, and extracted with ethyl acetate. The organic layer was neutralized with saturated potassium carbonate, washed with brine, dried and concentrated to give a dark oil. The oil was distilled to give 579 mg of dark oil which was then purified through silica gel column chromatography using 1:1 hexane to chloroform as eluent to give 327 mg of title compound as a yellow solid. ^1H NMR (CDCl_3) δ 0.92 (t, 3H), 1.14 (t, 3H), 1.2-1.4 (m, 2H), 1.45-1.60 (m, 2H), 1.85 (s, 3H), 2.16 (s, 6H), 2.30 (s, 3H), 2.33 (s, 3H), 3.2-3.4 (m, 4H), 5.8 (brs, 1H), 6.90 (s, 2H) ppm.

Example 2A. Butyl-(6-chloro-2-methyl-pyrimidin-4-yl)-ethylamine

A mixture of 2-methyl-4,6-dichloro-pyrimidine (1.63 g, 10 mmol) in 5ml of acetonitrile was treated with N-butyl-ethyl-amine (2.000 g, 20 mmol) and heated at reflux for 0.5 hours. The mixture was cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 2.271 g (100%) of title compound as a light-brown oil. ^1H NMR (CDCl_3) δ 0.93 (t, 3H), 1.13 (t, 3H), 1.22-1.36 (m, 2H), 1.45-1.6 (m, 2H), 2.43 (s, 3H), 3.25-3.60 (m, 4H), 6.15 (s, 1H) ppm.

B. N-Butyl-N-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of butyl-(6-chloro-2-methyl-pyrimidin-4-yl)-ethylamine (1.006 g, 4.42 mmol), and 2,4,6-trimethylaniline (3ml) was heated at reflux overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and 5 concentrated to give 2.862 g of a brown oil. The oil was purified through silica gel column chromatography to give 981 mg (68%) of title compound as a yellow oil. ^1H NMR (CDCl_3) δ 0.80 (t, 3H), 1.1-1.3 (m, 2H), 1.3-1.5 (m, 2H), 2.17 (s, 6H), 2.27 (s, 3H), 2.41 (s, 3H), 3.2 (m, 2H), 3.36 (m, 2H), 4.66 (s, 1H), 6.90 (s, 2H) ppm.

Example 3

10 A. Butyl-(6-chloro-2-methyl-5-ethyl-pyrimidin-4-yl)-ethylamine

A mixture of 2-methyl-5-ethyl-4,6-dichloro-pyrimidine (1.009 g, 5.28 mmol) in 5 ml of acetonitrile was treated with triethylamine (0.571 g, 5.65 mmol) and N-butyl-ethylamine (0.540 g, 5.31 mmol) and heated at reflux overnight. The mixture was diluted with water and dilute hydrogen chloride, and extracted with ethyl acetate. The organic 15 layer was neutralized with saturated potassium carbonate and washed with brine, dried and concentrated to give 1.193 g of yellow oil which was purified through silica gel column chromatography to give 1.157 g (86%) of title compound as a yellow oil. ^1H NMR (CDCl_3) δ 0.90 (t, 3H), 1.13 (t, 3H), 1.18 (t, 3H), 1.1-1.33 (m, 2H), 1.4-1.6 (m, 2H), 2.41 (s, 3H), 2.62 (q, 2H), 3.25-3.48 (m, 4H) ppm.

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B. N-Butyl-N-ethyl-2-methyl-5-ethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of butyl-(6-chloro-2-methyl-5-ethyl-pyrimidin-4-yl)-ethylamine (200 mg, 0.78 mmol) and 2,4,6-trimethylaniline (0.963 g, 7.1 mmol) was heated at reflux for 4 25 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated potassium carbonate and brine, dried and concentrated to give a dark oil. The oil was distilled to give 579 mg of the dark oil which was then purified through silica gel column chromatography using chloroform as eluent to give the title compound as a brown oil. ^1H NMR (CDCl_3) δ 0.93 (t, 3H), 1.14 30 (t, 3H), 1.1-1.4 (m, 4H), 1.45-1.60 (m, 2H), 2.17 (s, 6H), 2.30 (s, 3H), 2.33 (s, 3H), 3.2-3.4 (m, 4H), 6.90 (s, 2H) ppm.

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Example 4

2-Methyl-5-nitro-N,N'-bis-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of 2-methyl-5-nitro-4,6-dichloropyrimidine (0.513 g, 2.47 mmol) in 6 ml of acetonitrile was treated with 2,4,6-trimethylaniline (0.333 g, 2.46 mmol) and 5 triethylamine (1 ml) and stirred at room temperature for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 0.622 g of bright yellow solid. The solid was purified through silica gel column chromatography to give (6-chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(2,4,6-trimethylphenyl) amine and the title compound. ^1H NMR (CDCl_3) 10 for 6-(chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(2,4,6-trimethylphenyl)amine δ 2.16 (s, 6H), 2.33 (s, 3H), 2.43 (s, 3H), 6.95 (s, 2H), 8.79 (s, 1H) ppm. ^1H NMR (CDCl_3) for 2-methyl-5-nitro-N,N'-bis-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine: δ 2.11 (s, 3H), 2.22 (s, 12H), 2.33 (s, 3H), 6.96 (s, 4H), 10.44 (s, 2H) ppm.

Example 5

15 N-Butyl-N-ethyl-2-methyl-5-nitro-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of 6-(chloro-2-methyl-5-nitropyrimidin-4-yl)-(2,4,6-trimethyl-phenyl)amine (838 mg, 2.10 mmol) and N-ethyl-n-butyl-amine (555 mg, 5.48 mmol) in 15 ml acetonitrile was heated at reflux for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried 20 and concentrated to give 0.837 g of yellow oil. The solid was purified through silica gel column chromatography using 1:1 hexane to chloroform as eluent to give 753 mg of the title compound as a yellow oil. ^1H NMR (CDCl_3) δ 0.95 (t, 3H), 1.26 (t, 3H), 1.2-1.4 (m, 2H), 1.55-1.75 (m, 2H), 2.17 (s, 6H), 2.23 (s, 3H), 2.31 (s, 3H), 3.4-3.6 (m, 4H), 6.93 (s, 2H), 9.43 (s, 1H) ppm.

25 Example 6

The following compounds were prepared by a method analogous to that of Examples 3 or 5 starting with an appropriate amine and appropriate (6-chloro-2-methyl-5-substituted-pyrimidin-4-yl)-(2,4,6-trimethylphenyl)amine.

N-Propyl-N-ethyl-2-methyl-5-nitro-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-

30 diamine: ^1H NMR (CDCl_3) δ 0.93 (t, 3H), 1.26 (t, 3H), 1.6-1.8 (m, 2H), 2.17 (s, 6H), 2.23 (s, 3H), 2.31 (s, 3H), 3.4-3.55 (m, 4H), 6.93 (s, 2H), 9.41 (s, 1H) ppm.

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N-Butyl-5-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine: ^1H NMR (CDCl_3) δ 0.98 (t, 3H), 1.12 (t, 3H), 1.3-1.5 (m, 2H), 1.5-1.7 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 3.4-3.5 (m, 2H), 4.30 (brs, 1H), 5.65 (brs, 1H), 6.91 (s, 2H) ppm.

5-N-Diethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine: ^1H NMR 5 (CDCl_3) δ 1.09 (t, 3H), 1.25 (t, 3H), 2.17 (s, 3H), 2.30 (s, 3H), 2.31 (s, 3H), 3.4-3.6 (m, 2H), 4.35 (brs, 1H), 6.90 (s, 2H) ppm.

Example 7

N-Butyl-N-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,5,6-triamine

A mixture of N-butyl-N-ethyl-2-methyl-5-nitro-N'-(2,4,6-trimethylphenyl)-10 pyrimidine-4,6-diamine (242 mg, 0.65 mmol) and platinum oxide (35 mg) in 50 ml ethanol was hydrogenated at 40 psi for 24 hours. The mixture was filtered through celite and concentrated to dryness to give 217 mg of yellow oil. The oil was purified through silica gel column chromatography to give 135 mg (61%) of title compound. ^1H NMR (CDCl_3) δ 0.91 (t, 3H), 1.09 (t, 3H), 1.2-1.4 (m, 2H), 1.4-1.6 (m, 2H), 2.18 (s, 6H), 15 2.30 (s, 3H), 2.34 (s, 3H), 3.0 (brs, 2H), 3.1-3.3 (m, 4H), 5.89 (s, 1H), 6.92 (s, 2H) ppm.

Example 8

The following compounds were prepared by the method of Example 7 by hydrogenation of the corresponding 5-nitro derivatives.

N-Propyl-N-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,5,6-triamine:

20 ^1H NMR (CDCl_3) δ 0.89 (t, 3H), 1.09 (t, 3H), 1.45-1.60 (m, 2H), 2.18 (s, 6H), 2.30 (s, 3H), 2.34 (s, 3H), 3.80 (brs, 2H), 3.1-3.30 (m, 4H), 5.95 (brs, 1H), 6.92 (s, 2H) ppm.

2-Methyl-N,N'-bis-(2,4,6-trimethylphenyl)-pyrimidine-4,5,6-triamine:

25 ^1H NMR (CDCl_3) δ 2.04 (brs, 2H), 2.21 (s, 12H), 2.22 (s, 3H), 2.30 (s, 6H), 6.30 (s, 2H), 6.92 (s, 4H) ppm.

Example 9

6-(Ethyl-propyl-amino-2-methyl-9-(2,4,6-trimethylphenyl)-7,9-dihydropurin-8-one

A mixture of N-propyl-N-ethyl-2-methyl-N'-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5,6-triamine (120 mg, 0.35 mmol) and triethylamine (87 mg, 0.86 mmol) in 5 ml of dry tetrahydrofuran was treated with triphosgene (41 mg, 0.14 mmol) at 0°C. Precipitate 30 formed immediately and the reaction mixture was warmed to room temperature. After stirring for 30 minutes the mixture was filtered. The filtrate was concentrated to dryness to give 125 mg (100%) of title compound of a greenish color. ^1H NMR (CDCl_3) δ 0.90

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(t, 3H), 1.21 (t, 3H), 1.65 (m, 2H), 2.10 (s, 6H), 2.34 (s, 3H), 2.39 (s, 3H), 3.48 (dd, 2H), 3.58 (q, 2H), 6.99 (s, 2H), 9.63 (s, 1H) ppm.

Example 10

6-(Ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydropurin-8-one

5 A mixture of the title compound of Example 9 (54 mg, 0.15 mmol) in 3 ml of dry tetrahydrofuran was treated with sodium hydride (9 mg, 0.23 mmol, 60% in oil) at room temperature. The mixture was then treated with 0.02 ml of methyl iodide and stirred at room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 60 mg of brown
10 oil. The oil was purified through silica gel column chromatography using chloroform as eluent to give 56 mg of the title compound as a yellow oil which crystallized on standing. ¹H NMR (CDCl₃) δ 0.92 (t, 3H), 1.17 (t, 3H), 1.63 (m, 2H), 2.06 (s, 6H), 2.33 (s, 3H), 2.46 (s, 3H), 3.32 (dd, 2H), 3.40 (q, 2H), 3.63 (s, 3H), 7.00 (s, 2H) ppm.

Example 11

15 The following compounds were prepared by the method of Example 10 by reacting the title compound of Example 9 with an appropriate alkyl iodide.

7-Ethyl-6-(ethyl-propyl-amino)-2-methyl-9-(2,4,6-trimethylphenyl)-7,9-dihydropurin-8-one:

19 ¹H NMR (CDCl₃) δ 0.92 (t, 3H), 1.14 (t, 3H), 1.23 (m, 3H), 1.58 (m, 2H), 2.04 (s, 6H), 2.31 (s, 3H), 2.45 (s, 3H), 3.32 (dd, 2H), 3.36 (q, 2H), 4.08 (q, 2H), 7.00 (s, 2H) ppm.

6-(Ethyl-propyl-amino)-2-methyl-7-propyl-9-(2,4,6-trimethylphenyl)-7,9-dihydropurin-8-one:

24 ¹H NMR (CDCl₃) δ 0.87 (t, 3H), 0.90 (t, 3H), 1.15 (t, 3H), 1.5-12.8 (m, 4H), 2.05 (s, 6H), 2.33 (s, 3H), 2.47 (s, 3H), 3.32 (dd, 2H), 3.38 (q, 2H), 4.01 (q, 2H), 7.00 (s, 2H) ppm.

Example 12

[4-Chloro-2-methyl-6-(2,4,6-trimethylphenylamino)-pyrimidin-5-yl]-acetic acid ethyl ester

30 A mixture of (2-methyl-4,6-dichloro-pyrimidine-5-yl)-acetic acid ethyl ester (1.470 g, 5.9 mmol) and 2,4,6-trimethylaniline (2.56 ml, 17.7 mmol), in 15 ml of dimethylsulfoxide was heated at 120°C overnight and 138°C for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was

washed with brine, dried and concentrated to give a brown oil. The oil was purified through silica gel column chromatography to give 1.070 g (52%) of the title compound as a tan solid. ^1H NMR (CDCl_3) δ 1.30 (t, 3H), 2.14 (s, 6H), 2.32 (s, 3H), 2.37 (s, 3H), 3.79 (s, 2H), 4.23 (q, 2H), 7.00 (s, 2H), 7.02 (s, 1H) ppm.

5

Example 13

A. 4-Chloro-2-methyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

A mixture of the title compound of Example 12 (960 mg, 2.76 mmol) and p-toluene sulfonic acid (105 mg, 0.55 mmol) in 10 ml of toluene was heated at reflux 10 under Dean-Stark trap for 8 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 800 mg of a brown mass which was purified through silica gel column chromatography to give 348 mg (42%) of the title compound as a yellow powder. ^1H NMR (CDCl_3) δ 2.06 (s, 6H), 2.34 (s, 3H), 2.56 (s, 3H), 3.75 (s, 2H), 7.02 (s, 2H) ppm.

15

B. 4-(1-Hydroxymethyl-propylamino)-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidine-6-one

A mixture of the compound prepared under A (168 mg, 0.557 mmol) and (S)-2-amino-butanol (0.27 ml, 2.78 mmol) in 5 ml of dimethyl sulfoxide was heated at 145°C for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. 20 The organic layer was washed with brine, dried and concentrated to give an oil. The oil was purified through silica gel column chromatography, followed by recrystallization with diethyl ether to give 166 mg of the title compound as a grey solid.

^1H NMR (CDCl_3) δ 1.25 (t, 6H), 1.5-1.8 (m, 2H), 2.07 (s, 6H), 2.31 (s, 3H), 2.37 (s, 3H), 3.50 (s, 2H), 3.4-3.9 (m, 2H), 4.0 (m, 1H), 4.* (d, 1H), 7.00 (s, 2H) ppm.

25

Example 14

4-Diethylamino-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

The title compound was prepared by the method of Example 13B with diethylamine instead of (S)-2-amino-butanol. ^1H NMR (CDCl_3) δ 1.02 (t, 3H), 2.08 (s, 6H), 2.31 (s, 3H), 2.37 (s, 3H), 3.55 (q, 4H), 3.85 (s, 2H), 6.95 (s, 2H) ppm.

Example 15

A. 4-Chloro-2,5,5-trimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one and 4-Chloro-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

5 A mixture of 4-chloro-2-methyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (93 mg, 0.31 mmol) and sodium hydride (14 mg, 0.34 mmol, 60% in oil) in tetrahydrofuran (THF) was stirred for 5 minutes, then treated with an excess of methyl iodide and stirred for 1 hour. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried 10 and concentrated to give an oil. The oil was purified through silica gel column chromatography to give 32 mg of 4-chloro-2,5,5-trimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one and 64 mg of 4-chloro-2,5-dimethyl-7-(2,4,6-trimethyl)-phenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one.

15 ^1H NMR (CDCl_3) (4-chloro-2,5,5-trimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) δ 1.61 (s, 6H), 2.03 (s, 6H), 2.32 (s, 3H), 2.53 (s, 3H), 7.00 (s, 2H) ppm.

19 ^1H NMR (CDCl_3) (4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) δ 1.65 (d, 2H), 2.03 (s, 3H), 2.06 (s, 3H), 2.34 (s, 3H), 2.56 (s, 3H), 3.72 (q, 1H), 7.00 (s, 2H) ppm.

20 B. 4-(1-hydroxymethylpropylamino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

The title compound was prepared by the method of Example 13B from 4-chloro-2,5,5-trimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) and (S)-2-amino-butanol in dimethylsulfoxide at 140°C. ^1H NMR (CDCl_3) δ 1.02 (t, 3H), 1.53 (s, 6H), 1.5-1.8 (m, 2H), 2.04 (s, 6H), 2.32 (s, 3H), 2.38 (s, 3H), 3.6-3.9 (m, 2H), 4.0 (m, 1H), 4.5 (d, 1H), 5.25 (brs, 1H), 7.00 (s, 2H) ppm.

Example 16

5-Hydroxy-4-(1-hydroxymethylpropylamino)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

30 The title compound was prepared by the method of Example 13B from 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) and (S)-2-amino-butanol in dimethylsulfoxide (DMSO) at 140°C. Two diastereomers were obtained. The spectra for both diastereomers are shown below:

One isomer: ^1H NMR (CDCl_3) δ 1.03 (t, 3H), 1.55-1.75 (m, 2H), 1.77 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.32 (s, 3H), 2.37 (s, 3H), 3.55-3.85 (m, 2H), 4.0 (m, 1H), 5.1 (d, 1H), 5.3 (brs, 1H), 7.00 (s, 2H) ppm.

The other isomer: ^1H NMR (CDCl_3) δ 1.03 (t, 3H), 1.55-1.75 (m, 2H), 1.73 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.32 (s, 3H), 2.36 (s, 3H), 3.58 (dd, 1H), 3.77 (dd, 1H), 4.1 (m, 1H), 5.03 (d, 1H), 7.00 (s, 2H) ppm.

Example 17

5-Methoxy-4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

10 5-Hydroxy-4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one was prepared by the method analogous to that of Example 16 starting with 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) and N-butyl-ethyl-amine in DMSO at 140°C. Methylation of 5-hydroxy-4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-15 5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one with sodium hydride and methyl iodide using the method of Example 10 provides the title compound. ^1H NMR (CDCl_3) δ 6.97 (d, 2H), 3.5-4.0 (m, 4H), 3.23 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 2.12 (s, 3H), 2.03 (s, 3H), 1.69 (s, 3H), 1.6-1.8 (m, 2H), 1.3-1.5 (m, 2H), 1.24 (t, 3H), 0.99 (t, 3H) ppm.

Example 18

20 4-(Butyl-ethyl-amino)-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

The title compound was prepared by the method analogous to that of Example 13 (B) starting with 4-chloro-2-methyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) and N-butyl-ethyl-amine in DMSO at 135°C for 2.5 hours 25 to give an oil. ^1H NMR (CDCl_3) 7.00 (s, 2H), 3.85 (s, 2H), 3.62 (q, 2H), 3.53 (t, 2H), 2.35 (s, 3H), 2.32 (s, 3H), 2.10 (s, 3H), 1.55-1.70 (m, 2H), 1.35-1.50 (m, 2H), 1.25 (t, 3H), 1.00 (t, 3H) ppm.

Example 19

30 4-(Butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

A solution of 4-(butyl-ethyl-amino)-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (285 mg, 0.78 mmol) in 5 ml of dry THF was treated with lithium bis(trimethylsilyl)amide (1.05 mmol) at -78°C and stirred for 5

minutes. The mixture was quenched with methyl iodide (0.054 ml, 0.858 mmol) at -78°C. After stirring for 10 minutes, the mixture was warmed to 0°C and stirred at that temperature for 20 minutes. The mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, 5 dried and concentrated to give a purple form. The form was purified through silica gel column chromatography to give 4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (120 mg) as a purple glass, 4-(butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (35 mg) as a purple glass, and 98 mg of a mixture of the two 10 components as a purple glass.

15 ^1H NMR (CDCl₃) (4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) δ 6.96 (s, 2H), 3.7-3.9 (m, 2H), 3.51 (q, 1H), 3.15-3.4 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 1.53 (d, 3H), 1.5-1.65 (m, 2H), 1.3-1.4 (m, 2H), 1.17 (t, 3H), 0.95 (t, 3H) ppm.

15 ^1H NMR (CDCl₃) (4-(butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) δ 6.98 (s, 2H), 3.45 (q, 2H), 3.34 (t, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 2.06 (s, 6H), 1.55-1.7 (m, 2H), 1.3-1.45 (m, 2H), 1.23 (t, 3H), 0.99 (t, 3H) ppm.

Example 20

20 Butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethylamine

A solution of (4-butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) (111 mg, 0.292 mmol) in dry THF was treated with lithium aluminum hydride at room temperature. The resulting mixture was heated 25 at reflux for 5 hours. After standard work-up, 97 mg of crude material as an oil was obtained. The oil was purified through a chromatotron using 10% ethyl acetate in hexane as eluent to give butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethylamine as a clear pale yellow oil. ^1H NMR (CDCl₃) δ 6.91 (d, 2H), 3.7-3.9 (m, 2H), 3.2-3.4 (m, 4H), 2.5 (q, 1H), 2.28 (s, 6H), 2.22 (s, 3H), 30 2.05 (s, 3H), 1.5-1.7 (m, 2H), 1.3-1.5 (m, 5H), 1.17 (t, 3H), 0.97 (t, 3H) ppm. High MS (C₂₃H₃₄N₄) calc. 366.2776, found 366.27622.

Example 214-(Butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-6-ol

The title compound was prepared by the method of Example 20 starting from 5 (4-(butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) to give a pale yellow solid, mp 142-145°C; ^1H NMR (CDCl_3) δ 6.95 (d, 2H), 4.90 (s, 1H), 3.1-3.4 (m, 4H), 2.4 (brs, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H), 1.25-1.60 (m, 4H), 1.11 (t, 3H), 0.93 (t, 3H) ppm.

10

Example 22Butyl-ethyl-[6-methoxy-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]amine

To a solution of 4-(butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-6-ol] (20 mg, 0.05 mmol) in 1 ml of dry THF was 15 treated with sodium hydride (60% in oil, 4 mg, 0.1 mmol) and then methyl iodide (0.3 ml) was added at room temperature. After stirring at room temperature for 2.5 hours, the mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 26 mg of crude material. After silica gel column purification with 10% ethyl acetate in 20 hexane, 19 mg of a colorless oil of the title compound was obtained. ^1H NMR (CDCl_3) δ 6.92 (s, 1H), 6.89 (s, 1H), 4.48 (s, 1H), 3.1-3.3 (m, 4H), 3.11 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.4-1.52 (m, 2H), 1.2-1.4 (m, 2H), 1.10 (t, 3H), 0.90 (t, 3H) ppm.

Example 234-(Butyl-ethyl-amino)-2-methyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-5,6-dione

To a solution of 4-(butyl-ethyl-amino)-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (76 mg, 0.207 mmol), POCl_3 (0.039 ml, 0.415 mmol), triethylamine (0.059 ml), and dimethylamine (1 ml) in 2 ml acetonitrile was 30 heated at reflux for 1 hour. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a brown form (105 mg). After silica gel column chromatography, the title compound was isolated as a yellow glass (10 mg). ^1H NMR (CDCl_3) δ 7.00 (s, 2H), 3.95-4.15 (m, 2H), 3.65-3.85 (m,

2H), 2.38 (s, 3H), 2.32 (s, 3H), 2.10 (s, 6H), 1.55-1.75 (m, 2H), 1.35-1.55 (m, 2H), 1.25 (t, 3H), 1.00 (t, 3H) ppm.

Example 24

N-Butyl-N-ethyl-2,5,N'-trimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

5 A mixture of (6-chloro-2,5-dimethyl-pyrimidin-4-yl)-methyl-(2,4,6-trimethylphenyl)-amine (200 mg) and N-butyl-ethylamine (0.3 ml) in 1 ml of DMSO was heated in oil bath of 160°C for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give the crude material. After silica gel column purification using chloroform as eluent, the title 10 compound was obtained as an oil. ¹H NMR (CDCl₃) δ 6.83 (s, 2H), 3.22 (s, 3H), 3.12 (m, 4H), 2.44 (s, 3H), 2.26 (s, 3H), 2.01 (s, 6H), 1.35-1.42 (m, 2H), 1.1-1.25 (m, 2H), 1.00 (t, 3H), 0.90 (t, 3H) ppm.

Example 25

[2,5-Dimethyl-6-(tetrahydrofuran-3-yloxy)-pyrimidin-4-yl]-(2,4,6-trimethylphenyl)-amine

15 A mixture of 3-hydroxy-tetrahydrofuran (0.5 ml) and sodium hydride (60% in oil, 53 mg, 1.33 mmol) in dry THF was stirred at room temperature for 5 minutes, (6-chloro-2,5-dimethyl-pyrimidin-4-yl)-(2,4,6-trimethylphenyl)-amine (107 mg, 0.388 mmol) was added. The mixture was heated at reflux for 15 hours. The mixture was quenched with 20 water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a yellow oil. The oil was purified through silica gel column chromatography using 20% ethyl acetate in hexane as eluent to give 48 mg of the title compound as off-white crystals, mp 126-128°C. ¹H NMR (CDCl₃) δ 6.89 (s, 2H), 5.60 (brs, 2H), 3.8-4.0 (m, 4H), 2.27 (s, 6H), 2.13 (s, 6H), 2.1-2.25 (m, 2H), 1.93 (s, 3H) ppm.

25 Example 26

2-(S)-[2,5-Dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidin-4-ylamino]-butan-ol

A mixture of 4-chloro-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine (30 mg) and 2-(S)-amino-1-butanol (0.5 ml) in 0.5 ml of DMSO was heated at 130°C for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The 30 organic layer was separated, dried and concentrated to give a crude material. The crude residue was purified through silica gel column chromatography to give 24 mg of the title compound as white crystals. High MS for (C₁₉H₂₇N₃O₂) calc. 329.2103, found 329.21249; IR(KBr) 3400, 2940, 1580 cm⁻¹; ¹H NMR (CDCl₃) δ 6.841 (s, 2H), 5.72 (brs,

1H), 4.45 (d, 1H), 3.82-3.96 (m, 1H), 3.72-3.9 (m, 1H), 3.5-3.6 (m, 1H), 2.27 (s, 3H), 2.21 (s, 3H), 2.08 (s, 3H), 2.02 (s, 6H), 1.4-1.7 (m, 2H), 1.03 (t, 3H) ppm.

Example 27

4-(1-Ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine

5 A mixture of 3-pentanol (0.3 ml) and sodium hydride (60% in oil, 32 mg, 0.81 mmol) in DMSO was stirred at room temperature for 5 minutes. 4-Chloro-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine (150 mg, 0.54 mmol) was added and the resulting mixture was heated at 150°C for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and 10 concentrated to give a beige solid. The solid was purified through silica gel column chromatography using 20% chloroform in hexane as eluent to give the title compound as white crystals, mp 93.5-95.5°C. ¹H NMR (CDCl₃) δ 6.85 (s, 2H), 5.11 (t, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.11 (s, 3H), 2.03 (s, 6H), 1.68 (p, 4H), 0.92 (t, 6H) ppm.

Example 28

15 [(6-(Butyl-N-ethylamino)-2-methylpyrimidin-4-yl)-(2,4,6-trimethylphenyl)-amino]-acetic acid ethyl ester

A mixture of [(6-chloro-2-methylpyrimidin-4-yl)-(2,4,6-trimethylphenyl)-amino]-acetic acid ethyl ester (85 mg, 0.244 mmol) and N-butyl-ethylamine (0.17 ml, 1.1 mmol) in 4 ml DMSO was heated at 135°C for 15 hours. An additional 1 ml of N-butyl-20 ethylamine was added and the reaction was heated at that temperature for an additional 15 hours (tlc showed no starting material). The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give 123 mg of a light amber oil. The oil was purified through silica gel chromatotron using 5% ethyl acetate in hexane as eluent to give 92 mg (91%) of the title compound 25 as a white glass. ¹H NMR (CDCl₃) δ 6.94 (s, 2H), 4.69 (s, 1H), 4.23 (s, 2H), 4.22 (q, 2H), 3.35 (q, 2H), 3.15 (t, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 2.21 (s, 6H), 1.3-1.5 (m, 2H), 1.34 (t, 3H), 1.1-1.3 (m, 2H), 1.01 (t, 3H), 0.80 (t, 3H) ppm.

Example 29

4-(1-Ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

30 To a solution of 3-pentanol (0.2 ml, 0.5205 mol) in DMSO (1 ml) was added 60% sodium hydride in oil (30 mg) in a portionwise. After stirring at room temperature for 5 min, a solution of 4-chloro-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyridine (98 mg) in 0.5 ml of dry THF was added and the resulting mixture was heated at 130°C for

5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a yellow solid. The solid was purified through silica gel column chromatography using 20% chloroform in hexane to chloroform as eluent to give 7 mg of the title compound as white crystals, mp 72.5-5 74°C. ^1H NMR (CDCl_3) δ 6.84 (s, 2H), 6.26 (s, 1H), 4.16 (m, 1H), 2.27 (s, 3H), 2.17 (s, 6H), 2.04 (s, 6H), 1.69 (m, 4H), 0.95 (t, 6H) ppm.

The mesylate salt of 4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine was prepared by addition of 1 equivalent of methanesulfonic acid in ethyl acetate. The white crystals formed from ethyl acetate. Mp 117-119°C.

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Example 30[6-(Butyl-ethyl-amino)-2,5-dimethylpyrimidin-4-yl]-(2,4,6-trimethylphenyl)-acetonitrile

A solution of mesitylacetone (66 mg, 0.41 mmol) in 1 ml of DMSO was treated with NaH (60% in oil, 20 mg, 0.50 mmol) and stirred at room temperature for 20 15 minutes, butyl-(6-chloro-2,5-dimethylpyrimidin-4-yl)-ethylamine (100 mg, 0.414 mmol) was added and the resulting mixture was heated at 130°C for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give 160 mg of brown oil. The oil was purified through silica gel column chromatography using 5% ethyl acetate in hexane as eluent 20 to give the title compound as a brown oil. ^1H NMR (CDCl_3) δ 6.83 (s, 2H), 5.49 (s, 1H), 3.2-3.4 (m, 2H), 3.0-3.2 (m, 2H), 2.51 (s, 3H), 2.24 (s, 3H), 2.21 (s, 6H), 1.66 (s, 3H), 1.35-1.50 (m, 2H), 1.1-1.3 (m, 2H), 1.05 (t, 3H), 0.84 (t, 3H) ppm.

Example 312-[6-(1-Ethyl-propoxy)-2,5-dimethylpyrimidin-4-yl]-2-(2,4,6-trimethylphenyl)-propionitrile

To a solution of 3-pentanol (140 mg, 1.59 mmol) in 2 ml of dry THF was added sodium hydride (60% in oil, 38 mg) and the mixture was stirred at room temperature for 5 minutes. 2-(6-Chloro-2,5-dimethylpyrimidin-4-yl)-2-(2,4,6-trimethylphenyl)-propionitrile (100 mg, 0.319 mmol) was added to the reaction mixture, and the resulting mixture was 30 heated at reflux for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a brown oil (170 mg). The residue was purified through chromatotron using 20% ethyl acetate in hexane as eluent to give a mixture of two isomers as a yellow glass form and both having a M+ of 365 from GC/Ms. ^1H NMR (CDCl_3) δ 6.8 and 6.76 (s, 2H), 4.08 35 and 3.96 (m, 1H), 3.25 and 3.22 (s, 3H), 2.36 and 2.30 (s, 3H), 2.21, 2.20 and 2.06 (s, total of 9H), 1.5-1.7 (m, 4H), 1.04 (s, 3H), 0.96 and 0.90 (t, 3H) ppm.

Example 324-(1-Ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine

The title compound was prepared by the method analogous to that in Example 32 starting with 4-Chloro-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine and 3-pentanol. White crystals, mp. 82-84°C.

The title compounds of Example 33-39 were prepared by a method analogous to that of Example 27, starting with the appropriate 4-chloro-2-methyl-5-substituted 6-substituted-phenoxy)-pyrimidine and 3-pentanol.

Example 3310 4-(2,4-Dimethyl-phenoxy)-6-(1-ethyl-propoxy)-2,5-dimethyl-pyrimidine

¹H NMR (CDCl₃) δ 6.8-7.0 (m, 3H), 5.13 (m, 1H), 2.30 (s, 6H), 2.10 (s, 3H), 2.09 (s, 3H), 1.68 (m, 4H), 0.92 (t, 6H) ppm.

Example 3415 4-(2,6-Dimethyl-phenoxy)-6-(1-ethyl-propoxy)-2,5-dimethyl-pyrimidine

¹H NMR (CDCl₃) δ 7.04 (m, 3H), 5.12 (m, 1H), 2.25 (s, 3H), 2.13 (s, 3H), 2.07 (s, 6H), 1.66 (m, 4H), 0.92 (t, 6H) ppm.

Example 3520 4-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine-5-carbonitrile

mp 128-130°C, ¹H NMR (CDCl₃) δ 6.8 (s, 2H), 5.18 (m, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.00 (s, 6H), 1.4-1.58 (m, 4H), 0.90 (t, 6H) ppm.

Example 3625 5-tert-Butyl-4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

¹H NMR (CDCl₃) δ 6.85 (s, 2H), 5.25 (m, 1H), 2.29 (s, 3H), 2.20 (s, 3H), 2.03 (s, 6H), 1.65-1.80 (m, 4H), 1.52 (s, 9H), 0.90 (t, 6H) ppm.

Example 3730 4-(1-Ethyl-propoxy)-5-isopropyl-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

¹H NMR (CDCl₃) δ 6.85 (s, 2H), 5.17 (m, 1H), 3.50 (m, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 2.03 (s, 6H), 1.69 (m, 4H), 1.33 (s, 3H), 1.31 (s, 3H), 0.92 (t, 6H) ppm.

Example 3835 5-Bromo-4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

¹H NMR (CDCl₃) δ 6.86 (s, 2H), 5.16 (m, 1H), 2.29 (s, 3H), 2.28 (s, 3H), 2.06 (s, 6H), 1.65-1.80 (m, 4H), 1.52 (s, 9H), 0.95 (t, 6H) ppm.

Example 395-Chloro-4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

10 ^1H NMR (CDCl_3) δ 6.86 (s, 2H), 5.16 (m, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.06 (s, 6H), 1.65-1.80 (m, 4H), 1.52 (s, 9H), 0.94 (t, 6H) ppm.

15 The title compounds of Examples 40-41 were prepared by a method analogous to that described in Example 24, starting from 4-chloro-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine and the appropriate amine.

Example 40[2,5-Dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl](1-ethyl-propyl)-amine

10 ^1H NMR (CDCl_3) δ 6.84 (s, 2H), 4.10 (m, 2H, NH and CH), 2.27 (s, 3H), 2.21 (s, 3H), 2.04 (s, 9H), 1.3-1.6 (m, 4H), 0.91 (t, 6H) ppm.

Example 41Butyl-[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl]-ethyl-amine

15 ^1H NMR (CDCl_3) δ 6.87 (s, 2H), 3.76 (m, 2H), 3.68 (t, 2H), 2.73 (s, 3H), 2.28 (s, 6H), 1.99 (s, 6H), 1.5-1.7 (m, 4H), 1.27 (t, 3H), 0.94 (t, 3H) ppm.

15 The title compounds of Examples 42-54 were prepared by a method analogous to that described in Example 29, starting with the appropriate 4-chloro-2-methyl-6-(substituted phenoxy or thiophenoxy)-pyridine and the appropriate alcohol.

Example 422-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

20 ^1H NMR (CDCl_3) δ 7.18 (s, 2H), 6.30 (s, 1H), 4.22 (m, 1H), 2.20 (s, 6H), 2.05 (s, 6H), 1.73 (m, 4H), 1.00 (t, 6H) ppm.

Example 432-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

25 ^1H NMR (CDCl_3) δ 7.05 (s, 2H), 6.31 (s, 1H), 4.20 (m, 1H), 2.20 (s, 6H), 2.08 (s, 6H), 1.73 (m, 4H), 0.99 (t, 6H) ppm.

Example 443-Ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

30 ^1H NMR (CDCl_3) δ 6.85 (s, 2H), 6.26 (s, 1H), 4.18 (m, 1H), 2.73 (q, 2H), 2.28 (s, 3H), 2.17 (s, 3H), 2.05 (s, 6H), (m, 4H), 1.18 (t, 3H), 0.96 (t, 6H) ppm.

Example 454-(1-ethyl-propenyl)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (A mixture of cis and trans isomers)

35 ^1H NMR (CDCl_3) δ 6.85 (s, 2H), 6.30 (s, 0.3H), 6.21 (s, 0.7H), 5.10 (m, 0.7H), 4.95 (m, 0.3H), 2.27 (s, 3H), 2.24 (s, 2.1H), 2.19 (s, 0.9H), 2.14 (s, 3H), 2.05 (s, 6H), 1.65 (d, 0.9H), 1.50 (d, 2.1H), 1.08 (t, 1.8H), 1.05 (t, 4.2H) ppm.

Example 46Methanesulfonic acid salt of 4-(1-ethyl-propoxy)-2,3,5-trimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine

5 Mp 58-60°C. ^1H NMR (CDCl_3) δ 6.90 (s, 2H), 4.20 (m, 1H), 2.70 (s, 3H), 2.61 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.08 (s, 6H), 1.5-1.8 (m, 4H), 0.96 (t, 6H) ppm.

Example 474-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

10 ^1H NMR (CDCl_3) δ 6.84 (s, 2H), 6.39 (s, 1H), 5.04 (m, 1H), 3.85 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H), 2.05 (s, 6H), 1.5-1.7 (m, 4H), 0.95 (s, 6H) ppm.

Example 484-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyridine

15 ^1H NMR (CDCl_3) δ 6.90 (s, 2H), 6.34 (d, $J=2\text{Hz}$, 1H), 5.70 (d, $J=2\text{Hz}$, 1H), 4.05 (m, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.11 (s, 6H), 1.62 (m, 4H), 0.89 (t, 6H) ppm.

Example 493,6-Dimethyl-4-(tetrahydro-furan-3-yloxy)-2-(2,4,6-trimethyl-phenoxy)-pyridine

10 ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 6.25 (s, 1H), 4.99 (m, 1H), 3.9-4.1 (m, 4H), 2.31 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 2.1-2.3 (m, 2H), 2.07 (s, 6H) ppm.

Example 504-(1-Methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

15 ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 6.38 (s, 1H), 4.42 (m, 1H), 3.5-3.7 (m, 2H), 3.42 (s, 3H), 2.31 (s, 3H), 2.21 (s, 6H), 2.07 (s, 6H), 1.7-1.85 (m, 2H), 1.02 (t, 3H) ppm.

Example 513-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yloxy]-pentan-2-ol

20 ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 6.34 (s, 1H), 4.25-4.45 (m, 1H), 3.6-3.8 (m, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 2.06 (s, 6H), 1.2-1.4 (m, 5H), 1.07 (t, 3H) ppm.

Example 524-sec-Butoxy-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

25 ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 6.31 (s, 1H), 4.35 (m, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 2.07 (s, 6H), 1.7-1.9 (m, 2H), 1.34 (d, 3H), 1.01 (t, 3H) ppm.

Example 532-(2,4-Dimethyl-phenylsulfanyl)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

30 Golden oil. ^1H NMR (CDCl_3) δ 7.19 (d, $J=8\text{Hz}$, 1H), 7.06 (s, 1H), 6.94 (d, $J=8\text{Hz}$, 1H), 6.42 (s, 1H), 4.19 (m, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H), 2.18 (s, 3H), 1.69 (m, 4H), 0.95 (t, 6H) ppm.

Example 544-(1-Ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine

¹H NMR (CDCl₃) δ 6.97 (s, 2H), 6.30 (s, 1H), 4.15 (m, 1H), 2.35 (s, 6H), 2.30 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.68 (m, 4H), 0.95 (t, 6H) ppm.

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Example 552-(4-Ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

To a solution of 2.5 N n-BuLi in hexane (0.47 ml, 1.18 mmol) in 5ml of dry THF was added a solution of 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine (465 mg, 1.18 mmol) in 5 ml of dry THF at -78°C. After stirring at that 10 temperature for 5 min, an excess of ethyl iodide (0.4 ml) was added and the resulting mixture was stirred at -78°C for 30 min, then at 0°C for 15 min. The mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried and concentrated to give a light brown oil. The oil was purified through silica gel column chromatography using chloroform as eluent to give 260 mg 15 of the title compound as white solid. ¹H NMR (CDCl₃) δ 6.90 (s, 2H), 6.38 (s, 1H), 4.20 (m, 1H), 2.61 (q, 2H), 2.24 (s, 3H), 2.21 (s, 3H), 2.10 (s, 6H), 1.70 (m, 4H), 1.30 (t, 3H), 0.98 (t, 6H) ppm.

The title compounds of Examples 56-62 were prepared by a method analogous to that described in Example 55, starting from n-BuLi and 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine, followed by quenching with an appropriate electrophile.

Example 564-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzaldehyde

¹H NMR (CDCl₃) δ 9.94 (s, 1H), 7.61 (s, 2H), 6.32 (s, 1H), 4.20 (m, 1H), 2.21 (s, 25 3H), 2.16 (s, 9H), 1.70 (m, 4H), 0.98 (t, 6H) ppm.

Example 572-(2,6-Dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

¹H NMR (CDCl₃) δ 6.88 (s, 2H), 6.30 (s, 1H), 4.20 (m, 1H), 2.64 (dd, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.09 (s, 6H), 1.6-1.8 (m, 6H), 0.9-1.1 (m, 9H) ppm.

30

Example 582-(2,6-Dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

¹H NMR (CDCl₃) δ 7.06 (m, 3H), 6.30 (s, 1H), 4.20 (m, 1H), 2.21 (s, 6H), 2.11 (s, 6H), 1.73 (m, 4H), 0.99 (t, 6H) ppm.

Example 592-[4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl]-propan-2-ol

5 ¹H NMR (CDCl₃) δ 7.15 (s, 2H), 6.25 (s, 1H), 4.20 (m, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.10 (s, 6H), 1.85 (brs, 1H), 1.70 (m, 4H), 1.60 (s, 6H), 0.95 (t, 6H) ppm.

Example 604-(1-Ethyl-propoxy)-2-(4-iodo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

10 ¹H NMR (CDCl₃) δ 7.39 (s, 2H), 6.30 (s, 1H), 4.19 (m, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 2.05 (s, 6H), 1.72 (m, 4H), 0.98 (t, 6H) ppm.

Example 614-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol

15 ¹H NMR (CDCl₃) δ 7.85 (brs, 1H), 6.36 (s, 1H), 6.24 (s, 2H), 4.24 (m, 1H), 2.39 (s, 3H), 2.20 (s, 3H), 2.02 (s, 6H), 1.74 (m, 4H), 1.00 (t, 6H) ppm.

Example 621-[4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl]-pyrrolidin-2-one

20 ¹H NMR (CDCl₃) δ 7.30 (s, 2H), 6.30 (s, 1H), 4.20 (m, 1H), 3.88 (t, 2H), 2.61 (t, 2H) ppm.

Example 63{4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl}-methanol

25 A mixture of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzaldehyde (114 mg, 0.41 mmol) and sodium borohydride (63 mg, 1.6 mmol) in 3 ml of methanol was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give yellow oil. The oil was purified through silica gel using chloroform as eluent to give 70 mg of the title compound as a colorless oil. ¹H NMR (CDCl₃) δ 7.04 (s, 2H), 6.32 (s, 1H), 4.55 (s, 2H), 4.21 (m, 1H), 2.30 (brs, 1H), 2.22 (s, 3H), 2.21 (s, 3H), 2.12 (s, 6H), 1.73 (m, 4H), 0.91 (t, 6H) ppm.

Example 644-(1-Ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

30 To a solution of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol (40 mg, 0.12 mmol) in 3 ml of dry THF was added 10 mg of 60% sodium hydride in oil at room temperature. After stirring for 5 min, 0.3 ml of methyl iodide was added and the resulting mixture was stirred at room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid. The solid was purified through silica gel column

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chromatography using hexane to 1:1 chloroform:hexane as eluent to yield 20 mg of the title compound as yellow solid. ^1H NMR (CDCl_3) δ 6.66 (s, 2H), 6.28 (s, 1H), 4.20 (m, 1H), 3.79 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 2.08 (s, 6H), 1.71 (m, 4H), 0.97 (t, 6H) ppm.

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Example 65

4-(1-Ethyl-propoxy)-2-(4-isopropoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

To a solution of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol (58 mg, 0.176 mmol) in 3 ml of dry THF was added triphenylphosphine (70 mg, 0.264 mmol) and isopropanol (60 mg, 0.22 mmol). The resulting mixture was stirred at room temperature for 5 min, diethyl azodicarboxylate (46 mg, 0.264 mmol) was added. The mixture was stirred at room temperature overnight. An additional 20 mg of diethyl azodicarboxylate was added and the mixture was stirred for an additional 4 hours. The mixture was quenched with water and extracted with methylene chloride. The organic layer was dried and concentrated to give an oil. The oil residue was purified through silica gel column chromatography using 1:1 hexane:chloroform to 1:2 hexane:chloroform as eluent to give 38 mg (58%) of the title compound as a colorless oil. ^1H NMR (CDCl_3) δ 6.60 (s, 2H), 6.28 (s, 1H), 4.50 (m, 1H), 4.18 (m, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.07 (s, 6H), 1.71 (m, 4H), 1.34 (d, 6H), 0.98 (t, 6H) ppm.

The title compounds of Examples 66-67 were prepared by a method analogous to that described in Example 64, starting with an appropriate pyridine-3,5-dimethylphenol or pyridine-3,5-dimethyl-phenyl methanol with a base, followed by quenching with an appropriate alkyl halide.

Example 66

2-(4-Ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

25 ^1H NMR (CDCl_3) δ 6.60 (s, 2H), 6.28 (s, 1H), 4.19 (m, 1H), 3.99 (q, 2H), 2.19 (s, 3H), 2.18 (s, 3H), 2.07 (s, 6H), 1.74 (m, 4H), 1.40 (t, 3H), 0.97 (t, 6H) ppm.

Example 67

4-(1-Ethyl-propoxy)-2-(4-methoxymethyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

30 Mp 58-60 $^{\circ}\text{C}$. ^1H NMR (CDCl_3) δ 7.05 (s, 2H), 6.30 (s, 1H), 4.41 (s, 2H), 4.19 (m, 1H), 3.42 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 2.11 (s, 6H), 1.72 (m, 4H), 0.98 (s, 6H) ppm.

Example 68

[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine

35 A mixture of 4-chloro-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine (1.330 g, 4.822 mmol) and 20 ml of ethyl amine in 13 ml of 1-methyl-2-pyrrolidinone was heated

at 150°C at 250 psi overnight in a pressure reactor. The reaction was heated an additional 24 hours at 175°C and 300 psi. The reaction mixture cooled to room temperature and diluted with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a brown oil. The oil residue was purified through 5 silica gel column chromatography using chloroform to 2% methanol in chloroform as eluent to give 0.820 g (60%) of the title compound as a white solid, mp 115-116°C.

¹H NMR (CDCl₃) δ 6.87 (s, 2H), 6.11 (s, 1H), 3.85 (t, 1H), 3.24 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 2.13 (s, 3H), 2.08 (s, 6H), 1.32 (t, 3H) ppm.

The title compounds of Examples 69-71 were prepared by the method 10 analogous to that described in Example 68 starting with an appropriate 4-chloro-2-substituted phenoxy-pyridine and an appropriate amine.

Example 69

[3,6-Dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-[1-ethyl-propyl]-amine

Mp 108-110°C. ¹H NMR (CDCl₃) δ 6.95 (s, 2H), 6.09 (s, 1H), 3.63 (d, 1H), 3.28 (m, 1H), 2.36 (s, 6H), 2.30 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 1.4-1.75 (m, 4H), 0.93 (t, 6H) ppm. The hydrogen chloride salt, mp 148-150°C; ¹H NMR (CDCl₃) δ 6.95 (s, 2H), 6.30 (s, 1H), 5.75 (d, 1H), 3.38 (m, 1H), 2.69 (s, 3H), 2.33 (s, 6H), 2.28 (s, 3H), 2.02 (s, 3H), 1.72 (m, 4H), 0.93 (t, 6H) ppm.

Example 70

20 2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine; white solid

¹H NMR (CDCl₃) δ 7.04 (s, 2H), 6.13 (s, 1H), 3.88 (t, 1H), 3.24 (m, 2H), 2.17 (s, 3H), 2.17 (s, 3H), 2.08 (s, 6H), 1.32 (t, 3H) ppm.

Example 71

25 [3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-amine
Tan crystals, mp 114-116°C. ¹H NMR (CDCl₃) δ 6.94 (s, 2H), 6.12 (s, 1H), 3.76 (t, 1H), 3.21 (m, 2H), 2.35 (s, 6H), 2.30 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H), 1.29 (t, 3H) ppm.

Example 72

30 [3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine
To a solution of [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine (7.00 g, 24.6 mmol) in 100 ml of dry THF was added 1.0 M lithium bis(trimethylsilyl)amide in hexane (32 ml, 32 mmol) at -78°C. After stirring at that temperature for 10 min, the reaction mixture was treated with iodopropane (13 ml, 125 mmol) at -70°C. After stirring at that temperature for 20 min, the dry ice bath was removed and the reaction mixture was stirred at room temperature for 3 hours. The

reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give an oil. The oil residue was purified through silica gel column chromatography using 1:1 chloroform:hexane to chloroform as eluent to give 5.04 g (62.5%) of [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-5 ethyl-propyl-amine as yellow solid; ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 6.41 (s, 1H), 3.11(q,2H), 3.03(dd,2H), 2.30 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 2.07 (s, 6H), 1.55 (m, 2H), 1.08 (t, 3H), 0.90 (t, 3H) ppm. The corresponding HCl salt, white crystals; mp 167-169°C; ^1H NMR (MeOH-d_4) δ 7.00 (s, 2H), 6.75 (s, 1H), 3.54(q,2H), 3.43 (t, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H), 2.08 (s, 6H), 1.69 (m, 2H), 1.25 (t, 3H), 0.94 (t, 3H) 10 ppm;

The title compounds of Examples 73-79 were prepared by the method analogous to that described in Example 72 starting with an appropriate 2-(substituted phenoxy or thiophenoxy)-pyridin-4-yl-ethyl amine and a base (lithium bis(trimethylsilyl)amide or lithium diisopropylamide), followed by quenching with an 15 appropriate alkyl halide.

Example 73

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine

^1H NMR (CDCl_3) δ 6.87 (s, 2H), 6.40 (s, 1H), 3.10(q,4H), 2.30 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 2.06 (s, 6H), 1.08 (t, 6H) ppm. The HCl salt, white crystals, mp 180-181°C; ^1H NMR (CD_3OD) δ 7.01 (s, 2H), 6.78 (s, 1H), 3.58(q,4H), 2.38 (s, 3H), 2.32 (s, 6H), 2.10 (s, 6H), 1.28 (t, 6H) ppm.

Example 74

[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-methyl-amine

^1H NMR (CDCl_3) δ 6.86 (s, 2H), 6.38 (s, 1H), 3.05(q,2H), 2.75 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.06 (s, 6H), 1.18 (t, 3H) ppm. The HCl salt, mp 173-174°C.

Example 75

Butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine

^1H NMR (CDCl_3) δ 6.88 (s, 2H), 6.41 (s, 1H), 3.0-3.3 (m, 4H), 2.31 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 2.08 (s, 6H), 1.3-1.6 (m, 4H), 1.09 (t, 3H), 0.93 (t, 3H) ppm.

Example 76

Butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine

^1H NMR (CDCl_3) δ 7.03 (s, 2H), 6.39 (s, 1H), 3.09(q,2H), 3.01(dd,2H), 2.21 (s, 3H), 2.16 (s, 3H), 2.05 (s, 6H), 1.4-1.6 (m, 2H), 1.25-1.40 (m, 2H), 1.06 (t, 3H), 0.87 (t, 3H) ppm. The HCl salt, mp 177-178°C; ^1H NMR(DMSO-d_6) δ 7.20 (s, 2H), 6.74 (s, 1H),

3.1-3.4 (m, 4H), 2.24 (s, 3H), 2.17 (s, 3H), 2.00 (s, 6H), 1.4-1.6 (m, 2H), 1.25-1.40 (m, 2H), 1.05 (t, 3H), 0.86 (t, 3H) ppm.

Example 77

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine

5 ¹H NMR (CDCl₃) δ 7.04 (s, 2H), 6.41 (s, 1H), 3.11(q,2H), 3.00 (m, 2H), 2.24 (s, 3H), 2.17 (s, 3H), 2.07 (s, 6H), 1.54 (m, 2H), 1.08 (t, 3H), 0.90 (t, 3H) ppm. The HCl salt, white crystals, mp 74-76°C. ¹H NMR(CD3OD) δ 7.23 (s, 2H), 6.81 (s, 1H), 3.58(q,2H), 3.46 (m, 2H), 2.38 (s, 3H), 2.31 (s, 3H), 2.13 (s, 6H), 1.6-1.8 (m, 2H), 1.26 (t, 3H), 0.96 (t, 3H) ppm.

10 Example 78

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine

15 ¹H NMR (CDCl₃) δ 7.05 (s, 2H), 6.41 (s, 1H), 3.11(q,4H), 2.24 (s, 3H), 2.18 (s, 3H), 2.07 (s, 6H), 1.09 (t, 6H) ppm. The HCl salt, white crystals, mp 184-185°C. ¹H NMR(CD3OD) δ 7.23 (s, 2H), 6.81 (s, 1H), 3.56(q,4H), 2.37 (s, 3H), 2.33 (s, 3H), 2.12 (s, 6H), 1.26 (t, 6H) ppm.

Example 79

[3,6-Dimethyl-[2-(2,4,6-trimethyl-phenoxy)sulfanyl]-pyridin-4-yl]-ethyl-propyl-amine

20 ¹H NMR (CDCl₃) δ 6.95 (s, 2H), 6.45 (s, 1H), 3.02 (q,2H), 2.97 (dd,2H), 2.35 (s, 6H), 2.31 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.49 (m, 2H), 1.02 (t, 3H), 0.86 (t, 3H) ppm. The HCl salt, white crystals, mp 110-112°C; ¹H NMR (CDCl₃) δ 6.92 (s, 2H), 6.51 (s, 1H), 3.27 (q,2H), 3.19 (dd,2H), 2.84 (s, 3H), 2.32 (s, 6H), 2.28 (s, 3H), 1.82 (s, 3H), 1.52 (m, 2H), 1.15 (t, 3H), 0.84 (t, 3H) ppm.

Example 80

N-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-ethyl-2,2,2-trifluoro-

25 acetamide

To a solution of [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine (200 mg, 0.7 mmol) in dry methylene chloride was added triethylamine (0.1 ml, 0.73 mmol) and trifluoroacetic anhydride (0.11 ml, 0.74 mmol) and stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the crude material. The crude material was purified through silica gel column chromatography using 25% hexane in chloroform as eluent to give 225 mg (83%) of the title compound as white crystals, mp 110-111°C, ¹H NMR (CDCl₃) δ 6.91 (s, 2H), 6.57 (s, 1H), 4.16 (m, 1H), 3.39 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 35 1.26 (t, 3H) ppm.

Example 813,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine

To a solution of N-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-N-ethyl-
5 2,2,2-trifluoro-acetamide (292 mg, 0.77 mmol) in 15 ml of dry THF was added 2M
BH₃.DMS in THF (0.96 ml, 1.92 mmol) at room temperature. The resulting mixture was
heated at reflux overnight. The mixture was quenched with water and extracted with
ethyl acetate. The organic layer was dried and concentrated to give 300 mg of white
solid. The solid was recrystallized from hexane and 2 drops of methanol to give white
10 crystals (298 mg, 96%). ¹H NMR (CDCl₃) δ 6.85 (s, 2H), 6.47 (s, 1H), 3.70 (q, 2H), 3.25
(q, 2H), 2.32 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H), 2.05 (s, 3H), 1.13 (t, 3H) ppm. The HCl
salt, white crystals, mp 73-74°C. ¹H NMR (CD₃OD) δ 6.97 (s, 1H), 6.96 (s, 2H), 4.09
(q, 2H), 3.46 (q, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H), 2.05 (s, 6H), 1.17 (t, 3H)
ppm.

15

Example 824-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

A mixture of 4-chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester (500 mg, 1.56 mmol) and 1-ethyl-propyl-amine (0.8 ml) in 1 ml of DMSO was
20 heated at reflux for 15 hours. The mixture was quenched with sat. ammonium chloride
and extracted with ethyl acetate. The organic layer was dried and concentrated to give
445.6 mg of yellow solid. The solid was purified through silica gel column
chromatography using 1:1 ratio of chloroform:hexane as eluent to give (289 mg, 50%) of
the title compound as white crystals, mp 98-102°C; ¹H NMR (CDCl₃) δ 8.04 (d, 1H),
25 6.85 (s, 2H), 6.06 (s, 1H), 3.85 (s, 3H), 3.32 (m, 1H), 2.28 (s, 3H), 2.10 (s, 3H), 2.07 (s,
3H), 1.62 (m, 4H), 0.95 (t, 6H) ppm.

Example 834-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl-methanol

30 A mixture of 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester (220 mg, 0.594 mmol) and 1M lithium aluminum hydride in THF (4 ml,
4 mmol) in dry THF (3 ml) was heated at reflux for 10 min, then stirred at rt overnight.
The mixture was quenched with 0.3 ml of water, 0.3 ml of 2N NaOH, then 0.8 ml of
water and stirred at room temperature for 10 min. White solid formed and was filtered
35 through celite. The filtrate was concentrate to dryness to give 207 mg (100%) of the
title compound as white solid. ¹H NMR (CDCl₃) δ 6.83 (s, 2H), 6.06 (s, 1H), 4.96 (d,

1H,NH), 4.88 (d, 2H), 3.28 (m, 1H), 2.26 (s, 3H), 2.11 (s, 3H), 2.04 (s, 6H), 1.4-1.6 (m, 4H), 1.4 (t, 1H,OH), 0.93 (t, 6H) ppm.

Example 84

4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid

5 A mixture of 4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester (16 mg, 0.043 mmol) and lithium hydroxide (30 mg) in dioxane (1 ml) and water (1 ml) was stirred at rt over night. The mixture was quenched with water and adjusted to pH 7.0 and extracted with chloroform. The organic layer was dried and concentrated to give the crude material. The crude material was purified through silica 10 gel column chromatography using 10% ethyl acetate in chloroform as eluent to give 7 mg of the title compound as white solid. ¹H NMR (CDCl₃) δ 9.12 (d, 1H), 6.87 (s, 2H), 6.16 (s, 1H), 3.35 (m, 1H), 2.29 (s, 3H), 2.10 (s, 3H), 2.07 (s, 6H), 1.4-1.6 (m, 4H), 0.94 (t, 6H) ppm.

Example 85

15 [3-Chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine hydrogen chloride

To a solution of 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-methanol (40 mg, 0.117 mmol) in 0.3 ml of dry methylene chloride was added thionyl chloride (0.15 ml) and stirred at rt for 1 hr. The mixture was concentrated 20 to dryness and pumped in vacuo to give white glass form. The glass form was triturated with ether to give the title compound (47 mg, 100%) as a white solid. ¹H NMR (CDCl₃) δ 6.92 (s, 2H), 6.24 (s, 1H), 5.50 (d, 1H), 4.72 (s, 2H), 3.50 (m, 1H), 2.73 (s, 3H), 2.27 (s, 3H), 2.15 (s, 6H), 1.5-1.8 (m, 4H), 0.97 (t, 6H) ppm.

Example 86

25 [3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine

To a solution of [3-Chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine (35 mg, 0.088 mmol) in dry THF (0.5 ml) was added 1M lithium aluminum hydride in THF (0.3 ml, 0.3 mmol) and the resulting mixture was stirred at rt for 1.5 hours. The mixture was quenched with 0.1 ml of water, 0.1 ml of 2N NaOH and 30 0.3 ml of water and stirred for 5 min. The mixture was filtered and washed with THF. The filtrate was concentrated to dryness. The residue was dissolved in chloroform and dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give 28 mg (100%) of oil. The oil was purified through silica gel column chromatography using chloroform as eluent to give 26 mg of the title compound as an oil. ¹H NMR (CDCl₃) δ 35 6.85 (s, 2H), 6.08 (s, 1H), 3.72 (d, NH,1H), 3.35 (m, 1H), 2.30 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H), 2.05 (s, 6H), 1.45-1.75 (m, 4H), 0.98 (t, 6H) ppm. The corresponding HCl salt

was prepared and triturated with ether to give 20 mg of white solid. ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 6.19 (s, 1H), 4.98 (brs, 1H), 3.50 (m, 1H), 2.71 (s, 3H), 2.26 (s, 3H), 2.12 (s, 6H), 2.00 (s, 3H), 1.5-1.8 (m, 4H), 0.95 (t, 6H) ppm.

Example 87

5 (1-Ethyl-propyl)-[3-methoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine

To a solution of 4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-methanol (46 mg, 0.134 mmol) in dry THF (0.5 ml) was added 60% sodium hydride in oil (6 mg, 0.134 mmol) and stirred for 2 min. Methyl iodide (0.1 ml) was 10 added and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the title compound as an oil (40 mg, 84%). ^1H NMR (CDCl_3) δ 6.84 (s, 2H), 6.06 (s, 1H), 5.13 (d, 1H), 4.78 (s, 2H), 3.33 (s, 3H), 3.29 (m, 1H), 2.27 (s, 3H), 2.12 (s, 3H), 2.04 (s, 6H), 1.3-1.6 (m, 4H), 0.93 (t, 6H) ppm.

15 Example 88

(1-Ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine

To a mixture of (2-chloro-6-methyl-3-nitro-pyridin-4-yl)-(1-ethyl-propyl)-amine (80 mg, 0.31 mmol) and 2,4,6-trimethylphenol (43 mg, 0.31 mmol) in 2ml of dry THF was 20 added potassium tert-butoxide (35 mg, 0.31 mmol) and the resulting mixture was stirred at rt overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid. The solid was purified through silica gel column chromatography using 6:4 ratio of chloroform:hexane as eluent to give 91 mg (83%) of the title compound as yellow solid, mp 160-162°C. ^1H NMR (CDCl_3) δ 7.62 (d, 1H), 6.87 (s, 2H), 6.18 (s, 1H), 3.40 (m, 1H), 2.30 (s, 3H), 25 2.15 (s, 3H), 2.10 (s, 6H), 1.5-1.8 (m, 4H), 0.99 (t, 6H) ppm.

Example 89

N4-(1-Ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine

A mixture of (2-chloro-6-methyl-3-nitro-pyridin-4-yl)-(1-ethyl-propyl)-amine (250 mg, 0.97 mmol) and 2,4,6-trimethylaniline (262 mg, 1.94 mmol) in 4 ml of dry DMSO 30 was heated at 130°C overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow oil. The oil was purified through silica gel column chromatography to give 150 mg (43%) of the title compound as yellow solid, mp 104-107°C. ^1H NMR (CDCl_3) δ 10.36 (s, 1H), 35 9.24 (d, 1H), 6.93 (s, 2H), 5.86 (s, 1H), 3.45 (m, 1H), 2.32 (s, 3H), 2.18 (s, 6H), 2.13 (s, 3H), 1.55-1.80 (m, 4H), 0.99 (t, 6H) ppm.

Example 90N4-(1-Ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine

A mixture of (1-ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine (40 mg, 0.112 mmol) and 4 mg of 10% Pd /C in 10 ml of ethanol was 5 hydrogenated at 50 psi overnight. The mixture was filtered through Celite® and the filtrate was concentrated to dryness to give a light brown crystals which was purified through silica gel column chromatography using 1:1 chloroform:hexane as eluent to give the title compound as golden crystals (36 mg, 97%), mp 105-107°C. ¹H NMR (CDCl₃) δ 6.88 (s, 2H), 6.11 (s, 1H), 4.00 (brs, 1H), 3.28 (m, 1H), 3.10 (brs, 2H), 2.31 10 (s, 3H), 2.16 (s, 3H), 2.10 (s, 6H), 1.45-1.75 (m, 4H), 0.98 (t, 6H) ppm. The corresponding HCl salt was prepared as white solid, mp 174-178°C, ¹H NMR(D₂O) δ 7.09 (s, 2H), 6.63 (s, 1H), 3.65 (m, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.11 (s, 6H), 1.45-1.80 (m, 4H), 0.91 (t, 6H) ppm.

Example 91

15 [2-(4-Chloro-2,6-dimethyl-phenoxy)-6-methyl-3-nitro-pyridin-4-yl]-[1-ethyl-propyl]-amine

To a mixture of (2-chloro-6-methyl-3-nitro-pyridin-4-yl)-(1-ethyl-propyl)-amine (850 mg, 3.30 mmol) and 4-chloro-2,6-dimethylphenol (516 mg, 3.30 mmol) in 25 ml of dry THF was added potassium tert-butoxide (370 mg, 3.30 mmol) and the resulting mixture 20 was stirred at room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid (1.31 g). The solid was purified through silica gel column chromatography using 6:4 ratio of chloroform:hexane as eluent to give 1.10 g (88%) of the title compound as yellow solid, mp 152-154°C. ¹H NMR (CDCl₃) δ 7.65 (d, 1H), 7.05 (s, 2H), 6.21 (s, 1H), 3.41 (m, 1H), 2.15 (s, 3H), 2.11 (s, 6H), 1.5-1.8 (m, 4H), 0.99 (t, 6H) 25 ppm.

Example 922-(2,6-Dimethyl-phenoxy)-N4-(1-ethyl-propyl)-6-methyl-pyridine-3,4-diamine

30 A mixture of (1-ethyl-propyl)-[6-methyl-3-nitro-2-(4-chloro-2,6-dimethyl-phenoxy)-pyridin-4-yl]-amine (800 mg, 2.12 mmol) and 160 mg of 10% Pd /C in 150 ml of ethanol was hydrogenated at 50 psi overnight. The mixture was filtered through Celite® and the filtrate was concentrated to dryness to give a purple glass form (810 mg) which was purified through silica gel column chromatography using 1:1 chloroform:hexane as eluent to give the title compound as tan crystals (360 mg), mp 98-100°C. ¹H NMR (CDCl₃) δ 7.05 (m, 3H), 6.11 (s, 1H), 4.00 (brs, 1H), 3.28 (m, 1H), 3.09 (brs, 2H), 2.14 35 (s, 9H), 1.45-1.75 (m, 4H), 0.98 (t, 6H) ppm. The corresponding HCl salt was prepared

as white solid, mp 158-162°C, ^1H NMR(D_2O) δ 7.27 (s, 3H), 6.67 (s, 1H), 3.65 (m, 1H), 2.27 (s, 3H), 2.16 (s, 6H), 1.45-1.80 (m, 4H), 0.93 (t, 6H) ppm.

Example 93

N4-(1-Ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine

5 A mixture of N4-(1-ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine (40 mg, 0.112 mmol) and 8 mg of 10% palladium/carbon (Pd/C) in 20 ml of ethanol was hydrogenated at 50 psi overnight. The mixture was filtered through celite and the filtrate was concentrated to dryness to give a dark residue (40 mg). ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 5.97 (s, 1H), 4.32 (d, 1H), 3.28 (m, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.18 (s, 6H), 1.45-1.75 (m, 4H), 0.93 (t, 6H) ppm. The corresponding di-HCl salt was prepared as a tan solid, mp 213-216°C, ^1H NMR(DMSO-d_6) δ 11.1 (s, 1H), 8.48 (s, 1H), 6.98 (s, 2H), 6.73 (brs, 1H), 6.38 (s, 1H), 3.36 (m, 1H), 2.28 (s, 3H), 2.19 (s, 3H), 2.08 (s, 6H), 1.54 (m, 4H), 0.88 (t, 6H) ppm.

Example 94

15 2-(4-Chloro-2,6-dimethyl-phenoxy)-N4-(1-ethyl-propyl)-6-methyl-pyridine-3,4-diamine

16 A mixture of (1-ethyl-propyl)-[6-methyl-3-nitro-2-(4-chloro-2,6-dimethyl-phenoxy)-pyridin-4-yl]-amine (100 mg, 0.265 mmol) and iron (73 mg, 1.33 mmol) in 12 ml of $\text{AcOH}/\text{H}_2\text{O}$ (1:1) and heated at 60°C for 3 hours. The mixture was concentrated to dryness. The residue was diluted with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the title compound. ^1H NMR (CDCl_3) δ 7.04 (s, 2H), 6.12 (s, 1H), 3.60 (brs, 2H), 3.28 (m, 1H), 2.14 (s, 3H), 2.10 (s, 6H), 1.45-1.80 (m, 4H), 0.97 (t, 6H) ppm.

Example 95

25 N-(1-Ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-diamine

26 To a cooled solution of (6-chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(2,4,6-trimethyl-pyridin-3-yl)-amine (88 mg, 0.29 mmol) in 1 ml of dry THF was added 1-ethyl-propyl-amine (80 mg, 0.92 mmol) at -78°C. The mixture was stirred at that temperature for 3 hrs, then warmed to -10°C for 1 hour. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the title compound (88 mg, 86%) as an orange solid, mp 151-152°C. ^1H NMR (CDCl_3) δ 9.16 (d, 1H), 6.92 (s, 1H), 4.35 (m, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 1.5-1.80 (m, 4H), 0.94 (t, 6H) ppm.

Example 96(1-Ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-amine

A solution of 3-hydroxy-2,4,6-trimethylpyridine (41 mg, 0.3 mmol) in 1 ml of dry THF was treated with 60% sodium hydride in oil (13 mg, 0.3 mmol) at rt. The reaction mixture was cooled to -78°C and a solution of (6-chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(1-ethyl-propyl)-amine (78 mg, 0.3 mmol) in 1 ml of dry THF was added. The reaction was stirred at -78°C for 1 hour, quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 91 mg (84%) of white solid of the title compound, mp 134-135°C. ¹H NMR (CDCl₃) δ 8.30 (d, 1H), 6.89 (s, 2H), 4.30 (m, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.10 (s, 6H), 1.5-1.8 (m, 4H), 0.97 (t, 6H) ppm.

Example 972-(4-Chloro-2,6-dimethyl-phenoxy)-N4-(1-ethyl-propyl)-6-methyl-pyridine-3,4-diamine

A mixture of [2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-3-nitro-pyridin-4-yl]-(1-ethyl-propyl)-amine (810 mg, 2.14 mmol) and iron (Fe) (594 mg, 10.72 mmol) in 96 ml of 1:1 of AcOH:H₂O was heated at reflux for 2 hours. Additional Fe (600 mg) was added. The mixture was heated for an additional 1.5 hours. The reaction mixture was concentrated to dryness. The residue was quenched with water, basified to pH 9.0 and filtered through celite. The filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give the title compound as a yellow oil. The oil was purified through silica gel column chromatography using chloroform as eluent to give 570 mg of 2-(4-chloro-2,6-dimethyl-phenoxy)-N4-(1-ethyl-propyl)-6-methyl-pyridine-3,4-diamine as a tan solid, mp 72-74°C. ¹H NMR(CDCl₃) δ 7.04(s,2H), 6.11(s,1H), 4.03(d,1H), 3.30(m,1H), 3.07(s,1H), 2.14(s,3H), 2.10(s,6H), 1.4-1.75(m,4H), 0.97(t,6H)ppm. The corresponding di-HCl salt was prepared as a white solid, mp 208-210°C.

Example 98N-[4-(1-Ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-acetamide

A mixture of 2-(2,4,6-trimethyl-phenoxy)-N4-(1-ethyl-propyl)-6-methyl-pyridine-3,4-diamine (250 mg, 0.763 mmol), acetic anhydride (72 mg, 0.763 mmol) and triethylamine (77 mg, 0.763 mmol) in 5 ml of methylene chloride was stirred at room temperature for 3 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give 310 mg of the crude material. The crude material was purified through silica gel column

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chromatography using 2% methanol in chloroform as eluent to give 250 mg (89% yield) of N-[4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-acetamide as tan solid, mp 154-156°C. ^1H NMR(CDCl₃) δ 6.97(s,0.64H), 6.86(s,2H), 6.26(m,0.36H), 6.14(s,0.64H), 6.12(s,0.36H), 4.80(d,0.64H), 4.40(d,0.36H), 3.2-3.4(m,1H), 2.29(s,3H), 5 2.26(s,1.9H), 2.17(s,1.1H), 2.16(s,1.9H), 2.06(s,6H), 1.99(s,1.1H), 1.4-1.75(m,4H), 0.97(t,6H)ppm.

Example 99

N-[2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-pyridin-3-yl]-acetamide

10 The title compound (35 mg) was isolated as a side product from the reduction experiment described in the Example 97. Compound can be prepared by standard acylation method by reacting 2-(4-chloro-2,6-dimethyl-phenoxy)-N4-(1-ethyl-propyl)-6-methyl-pyridine-3,4-diamine with acetic anhydride and triethylamine in methylene chloride. A tan solid was prepared, mp 161-164°C. ^1H NMR(CDCl₃) δ 7.04(s,2H), 6.88(s,0.6H), 6.26(s,0.4H), 6.15(s,1H), 4.75(d,0.6H), 4.40(d,0.4H), 3.30(m,1H), 15 2.27(s,1.8H), 2.15(s,3H), 2.06(s,6H), 1.98(s,1.2H), 1.4-1.8(m,4H), 0.97(t,6H)ppm.

Example 100

1-Ethyl-3-[4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-urea

20 ^1H NMR(CDCl₃) δ 6.85(s,2H), 6.11(s,1H), 5.38(s,1H), 4.68(s,1H), 4.65(m,1H), 3.2-3.4(m,3H), 2.28(s,3H), 2.16(s,3H), 2.08(s,6H), 1.4-1.7(m,4H), 1.10(t,3H), 0.93(t,6H)ppm.

Example 101

N-[4-(1-Ethyl-propyl)-2-methyl-N''-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,5,6-triamine

25 The title compound was prepared by hydrogenation of N-(1-ethyl-propyl)-2-methyl-5-nitro-N''-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,5-diamine by the method analogous to that described in Example 93. ^1H NMR(CDCl₃) δ 6.9(s,1H), 6.25(brs,1H), 4.7(d,1H), 4.08(m,1H), 2.5(s,3H), 2.45(s,3H), 2.30(s,3H), 2.20(s,3H), 1.45-1.7(m,4H), 0.98(t,6H) ppm.

30 Example 102

N4-(1-Ethyl-propyl)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine-4,6-diamine

The title compound was prepared by hydrogenation of (1-ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl]-amine by the method analogous to that described in Example 93. ^1H NMR(CDCl₃) δ 6.88(s,2H), 4.52(d,1H), 4.10(m,1H), 35 2.94(brs,2H), 2.30(s,3H), 2.23(s,3H), 2.09(s,6H), 1.4-1.8(m,4H), 0.95(t,6H) ppm. The

corresponding HCl salt, mp 248-250°C. ^1H NMR(CD_3OD) δ 6.91(s,2H), 4.00(m,1H), 2.39(s,3H), 2.28(s,3H), 2.07(s,6H), 1.6-1.8(m,4H), 1.00(t,6H) ppm.

Example 103

[6-(1-Ethyl-propoxy)-2-methyl-5-nitro-pyrimidin-4-yl]-(2,4,6-trimethyl-phenyl)-amine

5 A mixture of 3-pentanol (0.5 ml) and 60% sodium hydride (NaH) in oil (89 mg, 2.22 mmol) in 2 ml of dry THF was stirred for 2 min, then treated with a solution of 6-(chloro-2-methyl-5-nitropyrimidin-4-yl)-(2,4,6-trimethylphenyl)-amine(350mg, 1.14mmol) in 3 ml of dry THF at -78°C and stirred at that temperature for 1 hour, then stirred at room temperature overnight. The mixture was quenched with water and extracted with 10 ethyl acetate. The organic layer was dried and concentrated to give the crude material which was purified through silica gel column chromatography using 2:1 of hexane/ CHCl_3 as eluent to give 331 mg (85%) of the title compound as a yellow solid, mp 112-113°C. ^1H NMR(CDCl_3) δ 9.48(brs,1H), 6.49(s,2H), 5.37(m,1H), 2.33(s,3H), 2.29(s,3H), 2.18(s,6H), 1.7-1.9(m,4H), 0.99(t,6H) ppm.

15 Example 104

N-(1-Ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-phenyl)-pyrimidine-4,6-diamine

The title compound was prepared by the method analogous to that described in Example 5 using 1-ethylpropylamine. ^1H NMR(CDCl_3) δ 10.48(s,1H), 9.25(d,1H), 20 6.94(s,2H), 4.37(m,1H), 2.32(s,3H), 2.21(s,3H), 2.18(s,6H), 1.5-1.8(m,4H), 0.97(t,6H) ppm.

Example 105

6-(1-Ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine

The title compound was prepared by the method analogous to that described 25 in Example 93 starting from [6-(1-ethyl-propoxy)-2-methyl-5-nitro-pyrimidin-4-yl]-(2,4,6-trimethyl-phenyl)-amine. ^1H NMR(CDCl_3) δ 6.92(s,2H), 5.96(s,1H), 5.12(m,1H), 2.85(brs,1H), 2.31(s,3H), 2.30(s,3H), 2.19(s,6H), 1.70(m,4H), 0.94(t,6H) ppm.

Example 106

6-(1-Ethyl-propoxy)-2-methyl-5-nitro-pyrimidin-4-yl]-(2,4,6-trimethyl-pyridin-3-yl)-30 amine

The title compound was prepared by the method analogous to that described in Example 103 starting from (6-chloro-2-methyl-5-nitropyrimidin-4-yl)-(2,4,6-trimethyl-pyridin-3-yl)-amine and sodium 3-pantanoxide. ^1H NMR(CDCl_3) δ 9.45(s,1H), 6.95(s,1H), 5.35(m,1H), 2.53(s,3H), 2.41(s,3H), 2.29(s,3H), 2.18(s,3H), 1.7-1.9(m,4H), 35 0.98(t,6H) ppm.

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Example 107

N-(1-Ethyl-propyl)-2-methyl-N''-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5,6-triamine

The title compound was prepared by the method analogous to that described in Example 93 starting from N-(1-ethyl-propyl)-2-methyl-5-nitro-N''-(2,4,6-trimethyl-phenyl)-pyrimidine-4,6-diamine. ^1H NMR(CDCl₃) δ 6.90(s,2H), 6.10(s,1H), 4.78(d,1H), 4.03(m,1H), 2.31(s,3H), 2.29(s,3H), 2.20(s,6H), 1.4-1.6(m,4H), 0.91(t,6H) ppm.

Example 108

6-(1-Ethyl-propoxy)-2-methyl-9-(2,4,6-trimethyl-phenyl)-7,9-dihydro-purin-8-one

A mixture of 6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine (182 mg, 0.554 mmol), triethylamine (39 mg, 0.388 mmol) and triphosgene (58 mg, 0.196 mmol) in 6 ml of dry THF was stirred at room temperature for 30 min. The mixture was quenched with water and extracted with chloroform. The organic layer was dried and concentrated to give 177 mg (90%) of the title compound as a white solid, mp 159-160°C. ^1H NMR(CDCl₃) δ 8.50(s,1H), 6.99(s,2H), 5.30(m,1H), 2.47(s,3H), 2.32(s,3H), 2.08(s,6H), 1.73(m,4H), 0.94(t,6H) ppm.

Example 109

6-(1-Ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,5-diamine

The title compound was prepared by the method analogous to that described in Example 93 starting from 6-(1-ethyl-propoxy)-2-methyl-5-nitro-pyrimidin-4-yl]--(2,4,6-trimethyl-pyridin-3-yl)-amine. ^1H NMR(CDCl₃) δ 6.89(s,1H), 5.97(s,1H), 5.29(m,1H), 2.90(brs,1H), 2.48(s,3H), 2.41(s,3H), 2.26(s,3H), 2.17(s,3H), 1.68(m,4H), 0.93(t,6H) ppm.

Example 110

25 6-(1-Ethyl-propylamino)-2-methyl-9-(2,4,6-trimethyl-phenyl)-7,9-dihydro-purin-8-one

The title compound was prepared by the method analogous to that described in Example 108 starting from N-(1-ethyl-propyl)-2-methyl-N''-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5,6-triamine. ^1H NMR(CDCl₃) δ 6.59(s,2H), 5.28(d,1H), 3.92(m,1H), 2.40(s,3H), 2.32(s,3H), 2.08(s,6H), 1.25-1.45(m,4H), 0.80(t,6H) ppm.

Example 111

N4-(1-Ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine and N4-(1-Ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine

5 To a solution of N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine (0.250 g, 0.763 mmol) in dry THF (6 ml) was treated with 1M LiN(SiMe₃)₂ in THF (1.0 ml, 1.0 mmol) at -78°C and stirred for 10 min. an excess of methyl iodide was added and the resulting mixture was stirred at room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate. The 10 organic layer was dried and concentrated to give a crude material. The crude material was purified through silica gel column chromatography using 5% ethyl acetate in hexane as eluent to give N4-(1-ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine and N4-(1-ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine.

15 N4-(1-Ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine: ¹H NMR(CDCl₃) δ 6.88(s,2H), 6.02(s,1H), 5.55(d,1H), 3.21(m,1H), 2.79(s,6H), 2.30(s,3H), 2.10(s,3H), 2.09(s,6H), 1.4-1.75(m,4H), 0.95(t,6H) ppm.

20 N4-(1-Ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine: ¹H NMR(CDCl₃) δ 6.89(s,2H), 6.10(s,1H), 4.84(d,1H), 3.30(m,1H), 2.98(s,1H), 2.72(s,3H), 2.32(s,3H), 2.16(s,3H), 2.12(s,6H), 1.45-1.70(m,4H), 0.99(t,6H) ppm.

Example 112

N4-(1-Ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyrimidine-3-chloro-4-amine

The title compound was prepared by the method analogous to those of Examples 33-39 starting from 3,4-dichloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyrimidine and 1-ethyl-propylamine. ¹H NMR(CDCl₃) δ 6.87(s,2H), 4.97(d,1H), 4.12(m,1H), 2.30(s,3H), 2.25(s,3H), 2.10(s,6H), 1.4-1.8(m,4H), 0.96(t,6H) ppm.

Example 113

Butyl-[2,8-dimethyl-9-(2,4,6-trimethyl-phenyl)-9H-purin-6-yl]-ethyl-amine

30 A mixture of N-butyl-N-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,5,6-triamine (105 mg, 0.63 mmol) and triethyl orthoacetate (0.204 g, 1.25 mmol) and 10 mg of p-TsOH in toluene was heated reflux overnight. The mixture was concentrated to dryness and the residue was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give yellow oil. The oil was purified 35 through silica gel column chromatography using 1:1 of hexane:chloroform as eluent to give the title compound. ¹H NMR(CDCl₃) δ 7.01(s,2H), 3.9-4.1(m,4H), 2.45(s,3H),

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2.35(s,3H), 2.20(s,3H), 1.91(s,6H), 1.6-1.8(m,2H), 1.35-1.5(m,2H), 1.29(t,3H), 0.99(t,3H)
ppm.

Preparation A

(6-Chloro-2,5-dimethylpyrimidin-4-yl)-(2,4,6-trimethylphenyl)-amine

5 A mixture of 2,5-dimethyl-4,6-dichloropyrimidine (1.77 g, 10 mmol) and trimethylaniline (2.70 g, 20 mmol) in 5 ml of DMSO was heated in an oil bath of 160°C for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give the crude material. After silica gel column purification, and trituration with hexane, white crystals (790 mg)
10 were obtained; high MS calc, 275.1185, found 275.11667; IR(KBr) 3290, 3240, 2900, 1540 cm⁻¹. ¹H NMR (CDCl₃) δ 6.91 (s, 2H), 5.85 (s, 1H), 2.33 (s, 3H), 2.87 (s, 3H), 2.24 (s, 3H), 2.12 (s, 6H) ppm.

Preparation B

(6-Chloro-2,5-dimethylpyrimidin-4-yl)-methyl-(2,4,6-trimethylphenyl)-amine

15 A solution of (6-chloro-2,5-dimethylpyrimidin-4-yl)-(2,4,6-trimethylphenyl)-amine (276 mg, 1 mmol) in dry THF (2 ml) was treated with sodium hydride (60% in oil, 60 mg, 1.5 mmol) at room temperature. After stirring for 2 minutes, an excess of methyl iodide (0.5 ml) was added and the resulting mixture was stirred at room temperature for 20 minutes. The mixture was quenched with saturated ammonium chloride and 20 extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a pale yellow solid (255 mg). ¹H NMR (CDCl₃) δ 6.85 (s, 2H), 3.26 (s, 3H), 2.50 (s, 3H), 2.27 (s, 3H), 2.03 (s, 6H), 1.39 (s, 3H) ppm.

Preparation C

4-Chloro-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine

25 A solution of 2,4,6-trimethylphenol (2.720 g, 20 mmol) in 60 ml of dry THF was treated with NaH (60% in oil, 1.200 g, 30 mmol) at room temperature. After stirring at room temperature for 15 minutes, 2,5-dimethyl-4,6-dichloropyrimidine (3.34 g, 20 mmol) was added and the resulting mixture was heated at reflux for 15 hours. The mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The 30 organic layer was dried and concentrated to give 5.4528 g of beige solid. The solid was recrystallized from isopropanol to give 5.1345 g of pale yellow solid, mp 86-87°C; high MS (C₁₅H₁₇ClN₂) calc. 276.1025, found 276.10359. ¹H NMR (CDCl₃) δ 6.87 (s, 2H), 2.37 (s, 6H), 2.28 (s, 3H), 2.01 (s, 6H) ppm.

Preparation D2,4-Dichloro-3,6-dimethylpyridine

A mixture of 2,4-dihydroxy-3,6-dimethylpyridine (2.86 g, 20.58 mmol), POCl_3 (15 ml) and N,N-diethylaniline (3.6 ml, 22.64 mmol) was heated at reflux for 3 hours. The mixture was cooled, poured into ice water and extracted with diethyl ether. The organic layer was dried and concentrated to give 3.02 g of the crude material. After silica gel column chromatography using chloroform as eluent, 1.3102 g of the title compound was obtained as a yellow oil. $^1\text{H NMR}$ (CDCl_3) δ 7.07 (s, 1H), 2.43 (s, 3H), 2.39 (s, 3H) ppm.

10

Preparation E4-Chloro-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

A solution of 2,4,6-trimethylphenol (450 mg, 3.31 mmol) in 2 ml of DMSO was treated with NaH (60% in oil, 180 mg, 4.5 mmol). After 5min, 2,4-Dichloro-3,6-dimethylpyridine (528 mg, 3 mmol) was added. The mixture was heated in the oil bath of 130°C for 6 hours. The mixture was quenched with water and extracted with EtOAc. The organic layer was dried and concentrated to give 812.5 mg of crude material with two regioisomers. After silica gel column chromatography using 1:1 of CHCl_3 :hexane as eluent, the title compound was isolated as white crystals (141 mg), mp 57-62°C; high MS for $\text{C}_{18}\text{H}_{18}\text{ClNO}$: calc, 275.1072, found 275.70172; IR(KBr) 2951, 2920, 1592, 1564 cm⁻¹; $^1\text{H NMR}$ (CDCl_3) δ 6.87 (s, 2H), 6.77 (s, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 2.18 (s, 3H), 2.03 (s, 6H) ppm. The regiochemistry was determined by X-ray structural analysis of the undesired regioisomer, 2-chloro-3,6-dimethyl-4-(2,4,6-trimethyl-phenoxy)-pyridine.

To a solution of 4-chloro-2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine 1-oxide (34 mg) in 1 ml dry methylene chloride was added 2M PCl_3 in methylene chloride (0.022 ml). After addition, the mixture was heated at reflux for 0.5 hours, cooled and concentrated to dryness. The residue was poured into ice-water and extracted with methylene chloride. The organic layer was washed with brine, neutralized with sat. sodium carbonate, dried and concentrated to give 47 mg of the crude material. The crude material was crystallized out upon standing to give 31 mg (95%) of white crystals of the title compound.

Preparation F(6-Chloro-2,5-dimethylpyrimidin-4-yl)-(2,4,6-trimethylphenyl)-acetonitrile

To a solution of mesitylacetonitrile (0.900 g, 5.65 mmol) in 8 ml dry THF was added sodium hydride (60% in oil, 0.250 g, 6.21 mmol) and the mixture was stirred at 5 room temperature for 40 minutes. 2,5-Dimethyl-4,6-dichloropyrimidine (1.000 g, 5.65 mmol) was added and the resulting mixture was heated at reflux for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 1.800 g of a yellow oil. The oil residue was purified through silica gel column chromatography using 10% ethyl acetate in hexane as eluent 10 to give 0.986 g (58.3%) of the title compound as a white solid, mp 100-102°C. ¹H NMR (CDCl₃) δ 6.86 (s, 2H), 5.60 (s, 1H), 2.69 (s, 3H), 2.25 (s, 3H), 2.18 (s, 6H), 1.92 (s, 3H) ppm.

Preparation G2-(6-Chloro-2,5-dimethylpyrimidin-4-yl)-2-(2,4,6-trimethylphenyl)-propionitrile

15 A solution of (6-chloro-2,5-dimethylpyrimidin-4-yl)-(2,4,6-trimethylphenyl)-acetonitrile (0.250 g, 0.834 mmol) in 4 ml of dry THF was cooled to -78°C and treated with lithium bistrimethylsilylamide (1.0 M in THF, 0.92 ml) and stirred at that temperature for 45 minutes. Methyl iodide (0.426 g, 3.00 mmol) was added. The reaction mixture was gradually warmed to room temperature and stirred for 1 hour. The reaction mixture 20 was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow oil. The oil residue was purified through silica gel chromatotron using ethyl acetate/hexane (4:6) as eluent to give 161 mg (62%) of yellow solid, mp 181-183°C. ¹H NMR (CDCl₃) δ 6.980 (s, 2H), 3.45 (s, 3H), 2.40 (s, 3H), 2.24 (s, 3H), 2.21 (s, 6H), 1.25 (s, 3H) ppm.

25 Preparation H

4-Hydroxy-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine

A mixture of 6-chloro-2,5-dimethylpyrimidin-4-yl)-(2,4,6-trimethylphenyl)-acetonitrile (1.5 g, 5.0 mmol) and 60ml of 85% phosphoric acid was heated at reflux for 2 hours. The mixture was cooled at rt and diluted with water and extracted with 30 chloroform. The organic layer was washed with brine, dried and concentrated to give 1.21 g (95%) of the title compound as a white solid, mp 260-262°C.

Preparation I4-Chloro-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine

A mixture of 4-hydroxy-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine (1.2 g, 35 4.68 mmol) and POCl₃ (25 ml) was heated at reflux for 1 hour. The mixture was cooled and evaporated to dryness. The residue was poured into ice-water and extracted with

ethyl acetate. The organic layer was washed with brine, dried and concentrated to dryness to give 1.24 g (97%) of golden crystals, mp 82-84°C.

Preparation J

The following compounds were prepared by the methods analogous to that in 5 Preparation C starting with 5-substituted-4,6-dichloro-2-methyl-pyrimidine and substituted phenol in tetrahydrofuran in the presence of a base (sodium hydride) at the temperature indicated below.

5-tert-Butyl-4-chloro-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

The reaction was carried out at reflux in THF to give white crystals, mp 70-72°C.
10 ^1H NMR (CDCl_3) δ 6.82 (s, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 1.96 (s, 6H), 1.60 (s, 9H) ppm.

4-Chloro-5-isopropyl-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

The reaction was carried at reflux in THF to give white crystals, mp 68-70°C.
10 ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 3.60 (m, 1H), 2.36 (s, 3H), 2.29 (s, 3H), 2.00 (s, 6H),
15 1.43 (s, 3H), 1.41 (s, 3H) ppm.

4,5-Dichloro-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

The reaction run at room temperature to give white crystals, mp 68-70°C. ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 2.41 (s, 3H), 2.29 (s, 3H), 2.04 (s, 6H) ppm.

4-Chloro-5-bromo-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

20 The reaction was run at 0°C to room temperature. ^1H NMR (CDCl_3) δ 6.88 (s, 2H), 2.41 (s, 3H), 2.29 (s, 3H), 2.03 (s, 6H) ppm.

4-Chloro-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine-5-carbonitrile

The reaction was run at -40°C to give yellow crystals, mp 89-91°C. ^1H NMR (CDCl_3) δ 6.89 (s, 2H), 2.51 (s, 3H), 2.29 (s, 3H), 2.04 (s, 6H) ppm.

25 Preparation K

2,4-Dichloro-3,6-dimethyl-pyridine 1-oxide

A mixture of 2,4-dichloro-3,6-dimethyl-pyridine (790 mg, 4.49 mmol) and 50% m-chloro-perbenzoic acid (1.544 g, 4.49 mmol) in 10 ml of chloroform was stirred at room temperature for 20 hours. The mixture was quenched with water, washed with 30 saturated sodium thiosulfate and saturated sodium carbonate, brine and extracted with chloroform. The organic layer was dried and concentrated to give 954 mg of crude material. The material was purified through silica gel to give 662 mg of the title compound as a white crystals, mp 131-132°C. ^1H NMR (CDCl_3) δ 7.22 (s, 1H), 2.51 (s, 3H), 2.47 (s, 3H) ppm.

Preparation L

The following compounds were prepared by the method analogous to that described in Preparation K starting with an appropriate 2,4-dichloro-pyridine and an oxidizing agent.

5 2,4-Dichloro-6-methyl-1-oxy-nicotinic acid methyl ester

M.p. 90-91.5°C. ^1H NMR (CDCl_3) δ 7.26 (s, 1H), 3.98 (s, 3H), 2.54 (s, 3H) ppm.

(2,4-Dichloro-6-methyl-1-oxy-pyridin-3-yl)methanol

M.p. 188-191°C. ^1H NMR (CDCl_3) δ 7.13 (s, 1H), 4.87 (d, 2H), 2.47 (s, 3H), 2.38 (t, 1H, OH) ppm.

10 2,4-Dichloro-3,5,6-trimethyl-pyridine 1-oxide

M.p. 146-148°C. ^1H NMR (CDCl_3) δ 2.57 (s, 3H), 2.49 (s, 3H), 2.38 (s, 3H) ppm.

2,4-Dichloro-6-methyl-pyridine 1-oxide

M.p. 100-102°C. ^1H NMR (CDCl_3) δ 7.42 (d, 1H), 7.22 (d, 1H), 2.55 (s, 3H) ppm.

15 Preparation M

4-Chloro-2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine-1-oxide

To a solution of 2,4,6-trimethylphenol (415 mg, 3.05 mmol) in dry THF (20 ml) was treated with 60% sodium hydride in oil (122 mg, 3.05 mmol) at room temperature.

After all H_2 was evolved, 2,4-dichloro-3,6-dimethyl-pyridine 1-oxide (585.4 mg, 3.05 mmol) was added and the resulting mixture was heated at reflux for 2 hours. The mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give solid. The solid was recrystallized from pet ether to give 802 mg (90%) of the title compound as white crystals, mp 106-107°C. ^1H NMR (CDCl_3) δ 7.04 (s, 1H), 6.78 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H), 2.06 (s, 6H) ppm.

Preparation N

The following compounds were prepared by the method analogous to that described in Preparation M starting with an appropriate 2,4-dichloro-pyridine-1-oxide with an appropriate phenol or thiophenol in the presence of a base (potassium tert-buoxide, sodium hydride, or potassium hydride) at temperature between room temperature to reflux in dry THF.

2-(4-Bromo-2,6-dimethyl-phenoxy)-4-chloro-3,6-dimethyl-pyridine 1-oxide

White crystals, mp 137-139°C. ^1H NMR (CDCl_3) δ 7.12 (s, 2H), 7.08 (s, 1H), 2.42 (s, 6H), 2.09 (s, 6H) ppm.

35 4-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine 1-oxide

^1H NMR (CDCl_3) δ 7.08 (s, 1H), 6.97 (s, 2H), 2.42 (s, 6H), 2.09 (s, 6H) ppm,

4-Chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-1-oxy-nicotinic acid methyl ester

1 1H NMR (CDCl₃) δ 7.04 (s, 1H), 6.78 (s, 2H), 3.48 (s, 3H), 2.52 (s, 3H), 2.22 (s, 3H), 2.08 (s, 6H) ppm.

4-Chloro-2,3,5-trimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine 1-oxide

5 White crystals, mp 132-134°C. 1H NMR (CDCl₃) δ 6.75 (s, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.04 (s, 6H) ppm.

4-Chloro-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyridine 1-oxide

White crystals, mp 191-193°C. 1H NMR (CDCl₃) δ 6.96 (s, 1H), 6.95 (s, 2H), 2.62 (s, 3H), 2.32 (s, 3H), 2.13 (s, 6H) ppm.

10 4-Chloro-2-(2,4-dimethyl-phenylsulfanyl)-3,6-dimethyl-pyridine 1-oxide

White crystals, mp 148-151°C. 1H NMR (CDCl₃) δ 7.23 (s, 1H), 7.02 (s, 1H), 6.88 (s, 2H), 2.46 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 2.27 (s, 3H) ppm.

4-Chloro-2-(2,4,6-trimethyl-phenylsulfanyl)-3,6-dimethyl-pyridine 1-oxide

White crystals, mp 132-134°C. 1H NMR (CDCl₃) δ 7.13 (s, 1H), 6.91 (s, 2H), 2.46 (s, 3H), 2.31 (s, 6H), 2.27 (s, 3H), 2.10 (s, 3H) ppm.

Preparation of O

The following compounds were prepared by the method analogous to that described in Preparation E, second paragraph, starting with an appropriate 4-chloro-6-substituted phenoxy-pyridine 1-oxide and phosphorous trichloride.

20 2-(4-Bromo-2,6-dimethyl-phenoxy)-4-chloro-3,6-dimethyl-pyridine

White crystals. 1H NMR (CDCl₃) δ 7.22 (s, 2H), 6.81 (s, 1H), 2.40 (s, 3H), 2.20 (s, 3H), 2.05 (s, 6H) ppm.

4-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

White crystals. 1H NMR (CDCl₃) δ 7.07 (s, 2H), 6.81 (s, 1H), 2.41 (s, 3H), 2.20 (s, 3H), 2.06 (s, 6H) ppm.

4-Chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

Yellow crystals, mp 122-125°C. 1H NMR (CDCl₃) δ 6.84 (s, 2H), 6.82 (s, 1H), 3.94 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 2.04 (s, 6H) ppm.

4-Chloro-2,3,5-trimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine

30 White crystals, mp 101-103°C. 1H NMR (CDCl₃) δ 6.85 (s, 2H), 2.39 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 2.01 (s, 6H) ppm.

4-Chloro-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyridine

White crystals, mp 46-48°C. 1H NMR (CDCl₃) δ 6.92 (s, 2H), 6.84 (s, 1H), 2.62 (s, 3H), 2.32 (s, 3H), 2.13 (s, 6H) ppm.

4-Chloro-2-(2,4-dimethyl-phenylsulfanyl)-3,6-dimethyl-pyridine

White crystals, mp 148-151°C. ^1H NMR (CDCl_3) δ 7.23 (s, 1H), 7.02 (s, 1H), 6.88 (s, 2H), 2.46 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 2.27 (s, 3H) ppm.

4-Chloro-2-(2,4,6-trimethyl-phenylsulfanyl)-3,6-dimethyl-pyridine

5 White crystals, mp 132-134°C. ^1H NMR (CDCl_3) δ 7.13 (s, 1H), 6.91 (s, 2H), 2.46 (s, 3H), 2.31 (s, 6H), 2.27 (s, 3H), 2.10 (s, 3H) ppm.

Preparation P2-Chloro-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester

A mixture of 2,4-dichloro-6-methyl-nicotinic acid methyl ester (2.228 g, 10.13 mmol) and 1-ethyl-propyl amine (1.762 g, 20.26 mmol) in DMSO (4 ml) was heated at 110°C for 5 hours, then at room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentratd to give 1.796 g of crude material. The crude material was purified through silica gel column chromatography using chloroform to 5% methanol in chloroform as eluent to give 1.167 g (43%) of the title compound as a colorless oil. ^1H NMR (CDCl_3) δ 7.14 (brs, 1H), 6.27 (s, 1H), 3.86 (s, 3H), 3.27 (m, 1H), 2.33 (s, 3H), 1.3-1.6 (m, 4H), 0.88 (t, 6H) ppm.

Preparation Q(2-Chloro-6-methyl-3-nitro-pyridin-4-yl)-(1-ethyl-propyl)-amine

20 A mixture of 2,4-dichloro-6-methyl-3-nitro-pyridine (250 mg, 1.21 mmol) and 1-ethyl-propyl amine (105 mg, 1.21 mmol) in DMSO (4 ml) was stirred at room temperature for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentratd to give 280 mg of yellow oil. The oil was purified through silical gel column chromatography using 65% chloroform in hexane as eluent to give 110 mg (35%) of the title compound as a yellow crystal, mp 82-84°C. ^1H NMR (CDCl_3) δ 6.57 (d, 1H), 6.46 (s, 1H), 3.39 (m, 1H), 2.42 (s, 3H), 1.4-1.8 (m, 4H), 0.94 (t, 6H) ppm

Preparation R(6-Chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(1-ethyl-propyl)-amine

30 A mixture of 2-methyl-5-nitro-4,6-dichloro-pyrimidine (208 mg, 1.00 mmol) and 1-ethyl-propyl-amine (87 mg, 1.03 mmol) in 2 ml of dry THF was stirred at -78°C for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give a green oil. The oil was purified through silica gel column chromatography using chloroform to 1:1 hexane/chloroform as eluent to give the title compound (93 mg, 35%). ^1H NMR (CDCl_3) δ 7.50 (brs, 1H), 4.29 (m, 1H), 2.51 (s, 3H), 1.4-1.8 (m, 4H), 0.92 (t, 6H) ppm.

Preparation S(6-Chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(2,4,6-trimethyl-pyridin-3-yl)-amine

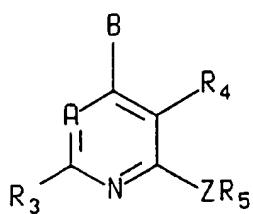
A solution of 2-methyl-5-nitro-4,6-dichloro-pyrimidine (208 mg, 1.00 mmol) in 2.5 ml of acetonitrile was treated with 2,4,6-trimethyl-3-amino-pyridine (273 mg, 2 mmol) 5 stirred at room temperature 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give red residue. The residue was purified through silica gel column chromatography using chloroform to 6% methanol in chloroform as eluent to give the title compound (110 mg, 36%) as an orange oil. ^1H NMR (CDCl_3) δ 8.78 (brs, 1H), 6.97 10 (s, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 2.17 (s, 3H) ppm.

-72-

CLAIMS

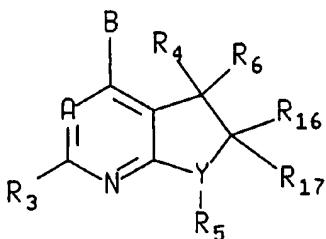
1. A compound of the formula

5



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I

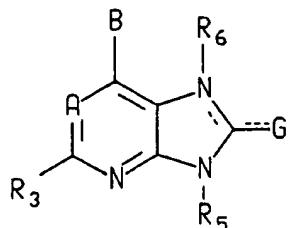


II

or

15

20



III

25

or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is -CR₁ or N;B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂,30 -CHR₂OR₁₂, -CHR₂SR₁₂, -C(S)R₂ or -C(O)R₂;G is oxygen, sulfur, NH, NH₃, hydrogen, methoxy, ethoxy, trifluoromethoxy, methyl, ethyl, thiomethoxy, NH₂, NHCH₃, N(CH₃)₂ or trifluoromethyl;

Y is -CH or N;

35 Z is NH, O, S, -N(C₁-C₂ alkyl) or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl;

R_1 is C_1 - C_6 alkyl which may optionally be substituted with one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3 , C_1 - C_4 alkoxy, -O-CO-(C_1 - C_4 alkyl), -O-CO-NH(C_1 - C_4 alkyl), -O-CO-N(C_1 - C_4 alkyl)(C_1 - C_2 alkyl), -NH(C_1 - C_4 alkyl), -N(C_1 - C_2 alkyl)(C_1 - C_4 alkyl), -S(C_1 - C_4 alkyl), -N(C_1 - C_4 alkyl)CO(C_1 - C_4 alkyl), -NHCO(C_1 - C_4 alkyl), -COO(C_1 - C_4 alkyl), -CONH(C_1 - C_4 alkyl), -CON(C_1 - C_4 alkyl)(C_1 - C_2 alkyl), CN, NO_2 , -SO(C_1 - C_4 alkyl) and -SO₂(C_1 - C_4 alkyl), and wherein said C_1 - C_6 alkyl and the (C_1 - C_4)alkyl moieties in the foregoing R_1 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1 - C_{12} alkyl, aryl or -(C_1 - C_4 alkylene)aryl wherein said aryl is phenyl, 10 naphthyl, thiienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C_1 - C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at 15 least 4 ring members and the cycloalkyl moiety of said -(C_1 - C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N- R_9 wherein R_9 is hydrogen or C_1 - C_4 alkyl; and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1 - C_4 alkyl, or with one substituent selected from bromo, iodo, C_1 - C_6 alkoxy, -O-CO-(C_1 - C_6 alkyl), -O-CO-N(C_1 - C_4 alkyl)(C_1 - C_2 alkyl), -S(C_1 - C_6 alkyl), CN, NO_2 , -SO(C_1 - C_4 alkyl), and -SO₂(C_1 - C_4 alkyl), and wherein 20 said C_1 - C_{12} alkyl and the C_1 - C_4 alkylene moiety of said -(C_1 - C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR₂R₂ or -CR₂R₂R₁₁ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which 25 one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3 , methylthio, methylsulfonyl, CH_2OH , or CH_2OCH_3 ;

R_4 is hydrogen, C_1 - C_4 alkyl, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, trifluoromethoxy, - CH_2OCH_3 , - $CH_2OCH_2CH_3$, - $CH_2CH_2OCH_3$, - CH_2OF , CF_3 , amino, nitro, 30 -NH(C_1 - C_4 alkyl), -N(CH_3)₂, -NHCOCH₃, -NHCONHCH₃, -SO_n(C_1 - C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C_1 - C_4 alkyl), -CHO, cyano or -COO(C_1 - C_4 alkyl) wherein said C_1 - C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C_1 - C_2 alkyl), -N(C_1 - C_2 alkyl)₂, -COO(C_1 - C_4 alkyl), -CO(C_1 - C_4 alkyl), C_1 - C_3 alkoxy, C_1 - C_3 35 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy, or with one substituent selected from

5 hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(C_1$ - C_6 alkyl) $O(C_1$ - C_6 alkyl), $-NHCH_3$, $-N(CH_3)_2$, $-COOH$, $-COO(C_1$ - C_4 alkyl), $-CO(C_1$ - C_4 alkyl), $-SO_2NH(C_1$ - C_4 alkyl), $-SO_2N(C_1$ - C_4 alkyl) $(C_1$ - C_2 alkyl), $-SO_2NH_2$, $-NHSO_2(C_1$ - C_4 alkyl), $-S(C_1$ - C_6 alkyl) and $-SO_2(C_1$ - C_6 alkyl), and wherein the C_1 - C_4 alkyl and C_1 - C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with

10 one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen or C_1 - C_6 alkyl, wherein said C_1 - C_6 alkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

R_7 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, $-O(C_1$ - C_4 alkyl), $-C(O)(C_1$ - C_4 alkyl), $-C(O)O(C_1$ - C_4 alkyl), $-OCF_3$, CF_3 , $-CH_2OH$, $-CH_2OCH_3$ or

15 $-CH_2OCH_2CH_3$;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

R_{12} is hydrogen or C_1 - C_4 alkyl; and

R_{16} and R_{17} are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that R_{16} and R_{17} are not both methoxy or ethoxy;

20 or R_{16} and R_{17} together form an oxo (=O) group;

with the proviso that when G is oxygen, sulfur, NH or NCH_3 , it is double bonded to the five membered ring of structure III, and with the further proviso that R_6 is absent when the nitrogen to which it is attached is double bonded to an adjacent ring carbon atom;

25 or a pharmaceutically acceptable salt of such compound.

2. A compound according to claim 1 wherein B is $-NR_1R_2$, $-NHCHR_1R_2$, $-SCHR_1R_2$ or $-OCHR_1R_2$; R_1 is C_1 - C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3 , or C_1 - C_2 alkoxy group and may optionally contain one double or triple bond; and R_2 is benzyl or C_1 - C_6 alkyl which may optionally contain one carbon-30 carbon double or triple bond, wherein said C_1 - C_6 alkyl or the phenyl moiety of said benzyl may optionally be substituted with fluoro, CF_3 , C_1 - C_2 alkyl, or C_1 - C_2 alkoxy.

3. A compound according to claim 1 wherein R_1 is C_1 - C_6 alkyl which may be substituted by fluoro, CF_3 , hydroxy, C_1 - C_2 alkyl or C_1 - C_2 alkoxy and which may optionally contain one carbon-carbon double or triple bond.

35 4. A compound according to claim 1 wherein R_2 is C_1 - C_4 alkyl which may optionally be substituted by fluoro, chloro, CF_3 , C_1 - C_4 alkyl or C_1 - C_4 alkoxy.

5. A compound according to claim 1 wherein R₃ is methyl, chloro, or methoxy.
6. A compound according to claim 1 wherein R₄ is methyl, -CH₂OH, cyano, trifluoromethoxy, methoxy, chloro, trifluoromethyl, -COOCH₃, -CH₂OCH₃, -CH₂Cl, -CH₂F, 5 ethyl, amino or nitro.
7. A compound according to claim 1 wherein R₅ is phenyl substituted with two or three substituents.
8. A compound according to claim 1 wherein R₆ is hydrogen, methyl or ethyl.
10. 9. A compound according to claim 1 wherein R₅ is pyridyl substituted with two or three substituents.
10. 10. A compound according to claim 7 wherein said substituents are selected, independently, from fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, trifluoromethyl, C₁-C₆ alkyl which may optionally be substituted with one hydroxy, C₁-C₄ alkoxy or fluoro 15 group and which may optionally contain one carbon-carbon double or triple bond, -(C₁-C₄ alkylene)O(C₁-C₂ alkyl), C₁-C₃ hydroxyalkyl, hydroxy, formyl, COO(C₁-C₂ alkyl), -(C₁-C₂ alkylene)amino, and -(C(O)(C₁-C₄ alkyl)).
11. 11. A compound according to claim 9 wherein said substituents are selected, independently, from fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, trifluoromethyl, 20 C₁-C₆ alkyl which may optionally be substituted with one hydroxy, C₁-C₄ alkoxy or fluoro group and which may optionally contain one carbon-carbon double or triple bond, -(C₁-C₄ alkylene)O(C₁-C₂ alkyl), C₁-C₃ hydroxyalkyl, hydroxy, formyl, -COO(C₁-C₂ alkyl), -(C₁-C₂ alkylene)amino, and -(C(O)(C₁-C₄ alkyl)).
12. 12. A compound according to claim 1, wherein said compound is 25 4-(1-ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine; 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine; 2-(4-ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine; 3-ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine; 30 2-(2,6-dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine; 4-(1-ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine; 2-(4-ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine; 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine; 35 4-(1-methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine; [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine; [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine; [2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl](1-ethyl-propyl)-amine;

butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine;
butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic
5 acid methyl ester;
[3,6-dimethyl-[2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-propyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-methanol;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine;
10 1-(ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
N4-(1-ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine;
N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-
15 amine;
N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine;
[3-chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)pyridin-4-yl]-[1-ethyl-propyl]-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-[1-ethyl-propyl]-amine;
20 (1-ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[3-methoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
(N-(1-ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-
25 diamine;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
N-butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine;
30 4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
N-butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-
35 amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

N4-(1-ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

5 N4-(1-ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine;

[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine; or
6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-

10 one;

or a pharmaceutically acceptable salt of one of the above compounds.

13. A pharmaceutical composition for the treatment of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder selected from 15 inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse 20 induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and 25 bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions; 30 muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder, and a pharmaceutically acceptable carrier.

14. A method for the treatment of (a) a disorder the treatment of which can 35 be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitator by CRF, or (b) a disorder selected from inflammatory disorders

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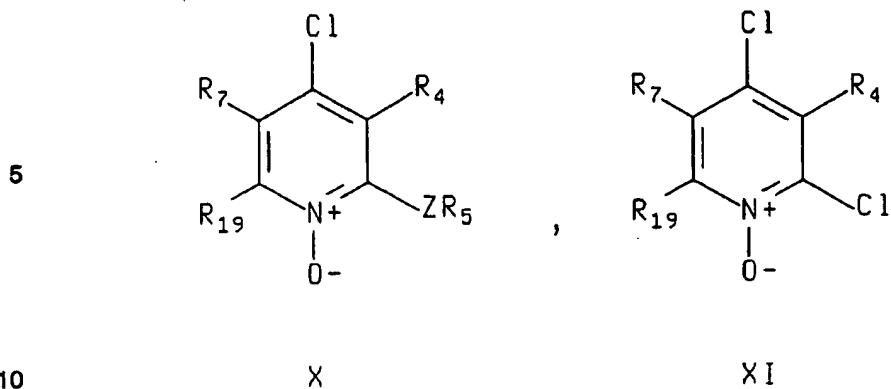
such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single 5 episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal 10 diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions; muscular spasms; urinary incontinence; 15 senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; and hypoglycemia in a mammal, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder.

20 15. A compound of the formula

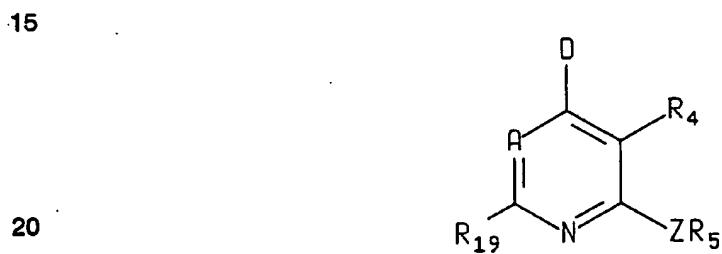
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or



IV

25 wherein R₇ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₄ alkyl), -C(O)(C₁-C₄ alkyl), -C(O)O(C₁-C₄ alkyl), -OCF₃, CF₃, -CH₂OH, -CH₂OCH₃ or -CH₂OCH₂CH₃;

D is chloro, hydroxy or cyano;

R₁₉ is methyl or ethyl;

30 R₅ is phenyl or pyridyl and R₅ is substituted by two or three substituents independently selected from C₁-C₄ alkyl, chloro and bromo, except that no more than one such substituent can be bromo;

R₄ is hydrogen, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, trifluoromethoxy, -CH₂OCH₃, -CH₂OCH₂CH₃, -CH₂CH₂OCH₃, -CH₂OF₃, CF₃, amino, nitro,

35 -NH(C₁-C₄ alkyl), -N(CH₃)₂, -NHCOPH₃, -NHCONHCH₃, -SO_n(C₁-C₄ alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C₁-C₄ alkyl), -CHO, cyano or -COO(C₁-C₄ alkyl) wherein

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said C₁-C₄ alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), C₁-C₃ alkoxy, C₁-C₃ thioalkyl, fluoro, chloro, cyano and nitro;

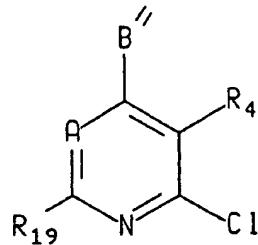
5 A is N, CH or CH₃;

and Z is O, NH, N(CH₃), S or CH₂, with the proviso that when A is CH or CCH₃, then Z must be O or S.

16. A compound according to claim 15 having the formula XI wherein R₁ is hydrogen or methyl and R₄ is hydrogen, C₁-C₄ alkyl, -O(C₁-C₄ alkyl), chloro or cyano.

10 17. A compound of the formula

15



X I I

20 wherein R₁₉ is methyl or ethyl;

R₄ is hydrogen, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, trifluoromethoxy, -CH₂OCH₃, -CH₂OCH₂CH₃, -CH₂CH₂OCH₃, -CH₂OF₃, CF₃, amino, nitro, -NH(C₁-C₄ alkyl), -N(CH₃)₂, -NHCOCH₃, -NHCONHCH₃, -SO_n(C₁-C₄ alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C₁-C₄ alkyl), -CHO, cyano or -COO(C₁-C₄ alkyl) wherein

25 said C₁-C₄ alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), C₁-C₃ alkoxy, C₁-C₃ thioalkyl, fluoro, chloro, cyano and nitro;

A is N, CH or CCH₃;

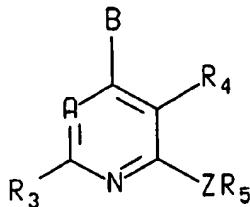
30 B'' is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁₂, -CHR₂SR₁₂, -C(S)R₂ or -C(O)R₂;

with the proviso that when A is CH or CCH₃, then B'' is -NR₁R₂, -NHR₁R₂, -OCHR₁R₂ or cyano and R₄ is an electron deficient group such as NO₂, -COO(C₁-C₄ alkyl), -C(=O)CH₃, -COOH or cyano.

35 18. A compound according to claim 17, wherein B'' is -NR₁R₂ or -NHCHR₁R₂ and A is CH or CH₃.

19. A process for preparing a compound of the formula I,

5



10

or a pharmaceutically acceptable salt thereof, wherein

A is -CR, or N;

B is -NR₁R₂, -NHCHR₁R₂, -OCHR₁R₂ or -SCHR₁R₂;

15 Z is NH, O, S, -N(C₁-C₂ alkyl) or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl;

20 R₁ is C₁-C₆ alkyl which may optionally be substituted with one or two substituents R₈ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF₃ and C₁-C₄ alkoxy, and wherein said C₁-C₆ alkyl and the C₁-C₄ alkyl moiety of said C₁-C₄ alkoxy may optionally contain one carbon-carbon double or triple bond;

25 R₂ is C₁-C₁₂ alkyl, aryl or -(C₁-C₄ alkylene)aryl wherein said aryl is phenyl, naphthyl, thiienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C₁-C₆ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C₁-C₆ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R₉ wherein R₉ is hydrogen or C₁-C₄ alkyl; and wherein each of the foregoing

30 R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C₁-C₄ alkyl, or with one substituent selected from bromo, iodo, C₁-C₆ alkoxy, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), CN, NO₂, -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), and wherein said C₁-C₁₂ alkyl and the C₁-C₄ alkylene moiety of said -(C₁-C₄ alkylene)aryl may

35 optionally contain one carbon-carbon double or triple bond;

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or $-\text{NR}_1\text{R}_2$ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl or ethyl;

5 R_4 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, fluoro, chloro, bromo, iodo, $\text{C}_1\text{-C}_4$ alkoxy, trifluoromethoxy, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OF}_3$, CF_3 , amino, nitro, $-\text{NH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOCH}_3$, $-\text{NHCONHCH}_3$, $-\text{SO}_n(\text{C}_1\text{-C}_4\text{ alkyl})$ wherein n is 0, 1 or 2, cyano, hydroxy, $-\text{CO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CHO}$, cyano or $-\text{COO}(\text{C}_1\text{-C}_4\text{ alkyl})$ wherein said $\text{C}_1\text{-C}_4$ alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, $-\text{NHCOCH}_3$, $-\text{NH}(\text{C}_1\text{-C}_2\text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_2\text{ alkyl})_2$, $-\text{COO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ thioalkyl, fluoro, chloro, cyano and nitro;

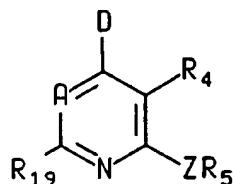
10 R_5 is phenyl or pyridyl and R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, $\text{C}_1\text{-C}_6$ alkyl, and $\text{C}_1\text{-C}_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(\text{C}_1\text{-C}_6\text{ alkyl})\text{O}(\text{C}_1\text{-C}_6\text{ alkyl})$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{COOH}$, $-\text{COO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})(\text{C}_1\text{-C}_2\text{ alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{NHSO}_2(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{S}(\text{C}_1\text{-C}_6\text{ alkyl})$ and $-\text{SO}_2(\text{C}_1\text{-C}_6\text{ alkyl})$, and wherein the $\text{C}_1\text{-C}_4$ alkyl and $\text{C}_1\text{-C}_6$ alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl; and

R_7 is hydrogen or methyl;

or a pharmaceutically acceptable salt of such compound;

comprising reacting a compound of the formula

25



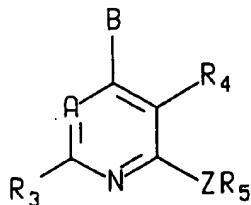
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IV

wherein R_{19} is methyl or ethyl, D is chloro and A , R_4 and R_5 are defined as above, with a compound of the formula BH , wherein B is defined as above, in the presence of a base; and then optionally converting the compound of formula I formed in such reaction into a pharmaceutically acceptable salt.

20. A process for preparing a compound of the formula

5



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or a pharmaceutically acceptable salt thereof, wherein

A is -CR₁ or N;

B is -NR₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁₂, -CHR₂SR₁₂, -C(S)R₂ or -C(O)R₂;

15 Z is NH, O, S, -N(C₁-C₂ alkyl) or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl;

20 R₁ is C₁-C₆ alkyl which may optionally be substituted with one or two substituents R₈ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF₃ and C₁-C₄ alkoxy, and wherein said C₁-C₆ alkyl and the C₁-C₄ alkyl moiety of said C₁-C₄ alkoxy may optionally contain one carbon-carbon double or triple bond;

25 R₂ is C₁-C₁₂ alkyl, aryl or -(C₁-C₄ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C₁-C₆ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C₁-C₆ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom

30 or by N-R₉ wherein R₉ is hydrogen or C₁-C₄ alkyl; and wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C₁-C₄ alkyl, or with one substituent selected from bromo, iodo, C₁-C₆ alkoxy, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), CN, NO₂, -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), and wherein

35 said C₁-C₁₂ alkyl and the C₁-C₄ alkylene moiety of said -(C₁-C₄ alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

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or $-\text{NR}_1\text{R}_2$ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

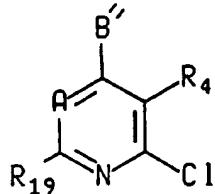
5 R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3 , methylthio, methylsulfonyl, CH_2OH , or CH_2OCH_3 ;

10 R_4 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, fluoro, chloro, bromo, iodo, $\text{C}_1\text{-C}_4$ alkoxy, trifluoromethoxy, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OF}_3$, CF_3 , amino, nitro, $-\text{NH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOC}_3$, $-\text{NHCONHCH}_3$, $-\text{SO}_n(\text{C}_1\text{-C}_4\text{ alkyl})$ wherein n is 0, 1 or 2, cyano, hydroxy, $-\text{CO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CHO}$, cyano or $-\text{COO}(\text{C}_1\text{-C}_4\text{ alkyl})$ wherein 15 said $\text{C}_1\text{-C}_4$ alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, $-\text{NHCOC}_3$, $-\text{NH}(\text{C}_1\text{-C}_2\text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_2\text{ alkyl})_2$, $-\text{COO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ thioalkyl, fluoro, chloro, cyano and nitro;

15 R_5 is phenyl or pyridyl, and R_6 is substituted with from one to three substituents independently selected from fluoro, chloro, $\text{C}_1\text{-C}_6$ alkyl, and $\text{C}_1\text{-C}_6$ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(\text{C}_1\text{-C}_6\text{ alkyl})\text{O}(\text{C}_1\text{-C}_6\text{ alkyl})$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{COOH}$, $-\text{COO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})(\text{C}_1\text{-C}_2\text{ alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{NHSO}_2(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{S}(\text{C}_1\text{-C}_6\text{ alkyl})$ and $-\text{SO}_2(\text{C}_1\text{-C}_6\text{ alkyl})$, and wherein the $\text{C}_1\text{-C}_4$ alkyl 20 and $\text{C}_1\text{-C}_6$ alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl; and

25 R_7 is hydrogen or methyl;
with the proviso that when A is CH or CCH_3 , then R_4 is an electron deficient group such as NO_2 , $-\text{COO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{C}(=\text{O})\text{CH}_3$, $-\text{COOH}$ or CN ;
or a pharmaceutically acceptable salt of such compound;
comprising reacting a compound of the formula

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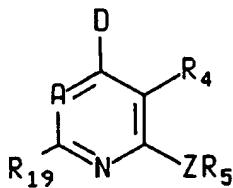
XII

wherein R_{19} is methyl or ethyl and A is N, CH or CCH_3 ; and wherein when A is N, then B'' and R_4 are defined, respectively, as B and R_4 are defined as above, and when A is CH or CH_3 , then B'' is $-NR_1R_2$, $-NHR_1R_2$, $-OCHR_1R_2$ or cyano and R_4 is an electron deficient group such as NO_2 , $-COO(C_1-C_4\text{ alkyl})$, $-C(=O)CH_3$, $-COOH$ or CN;

5 with a compound of the formula R_5ZH , wherein R_5 and Z are defined as above, and then optionally converting the compound of formula I formed in such reaction into a pharmaceutically acceptable salt.

21. A process according to claim 20 wherein R_4 in both the compound of formula I and the compound of formula IV is nitro.

10 22. A process for preparing a compound of the formula



IV

wherein R_{19} is methyl or ethyl;

20 D is chloro;

A is $-CR_1$ or N;

Z is NH, O, S, $-N(C_1-C_2\text{ alkyl})$ or $-C(R_{13}R_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

25 R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2OF_3$, CF_3 , amino, nitro, $-NH(C_1-C_4\text{ alkyl})$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHCONHCH_3$, $-SO_n(C_1-C_4\text{ alkyl})$ wherein n is 0, 1 or 2, cyano, hydroxy, $-CO(C_1-C_4\text{ alkyl})$, $-CHO$, cyano or $-COO(C_1-C_4\text{ alkyl})$ wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, $-NHCOCH_3$, $-NH(C_1-C_2\text{ alkyl})$, $-N(C_1-C_2\text{ alkyl})_2$, $-COO(C_1-C_4\text{ alkyl})$, $-CO(C_1-C_4\text{ alkyl})$, C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro; and

30 R_5 is phenyl or pyridyl, and R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_8 alkyl, and C_1-C_6 alkoxy, or with one

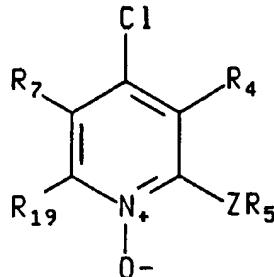
35 substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(C_1-C_6\text{ alkyl})O(C_1-C_6\text{ alkyl})$, $-NHCH_3$, $-N(CH_3)_2$, $-COOH$, $-COO(C_1-C_4\text{ alkyl})$,

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-CO(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NSO₂(C₁-C₄ alkyl), -S(C₁-C₆ alkyl) and -SO₂(C₁-C₆ alkyl), and wherein the C₁-C₄ alkyl and C₁-C₆ alkyl moieties of the foregoing R₅ groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino,

5 methylamino, dimethylamino and acetyl;

comprising reacting a compound of the formula

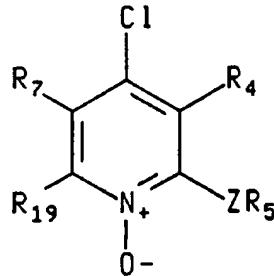


15

X

wherein R₁₉, R₄ and R₅ are defined as above and R₇ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₄ alkyl), -C(O)(C₁-C₄ alkyl), -C(O)O(C₁-C₄ alkyl), -OCF₃, CF₃, -CH₂OH, -CH₂OCH₃ or -CH₂OCH₂CH₃, with phosphorus trichloride.

20 23. A process for preparing a compound of the formula



30

X

wherein R₁₉ is methyl or ethyl;

A is -CR₇ or N;

Z is O, S or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or

35 methyl;

R_4 is hydrogen, C_1 - C_4 alkyl, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2OF_3$, CF_3 , amino, nitro, $-NH(C_1$ - C_4 alkyl), $-N(CH_3)_2$, $-NHCOCH_3$, $-NHCONHCH_3$, $-SO_n(C_1$ - C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, $-CO(C_1$ - C_4 alkyl), $-CHO$, cyano or $-COO(C_1$ - C_4 alkyl) wherein

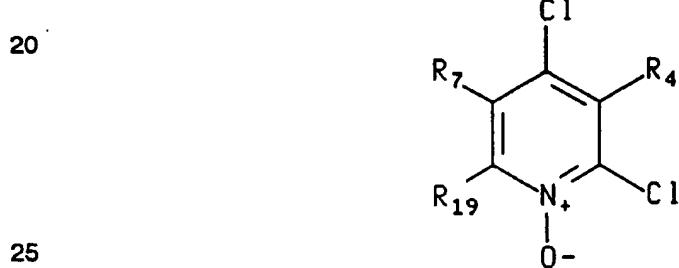
5 said C_1 - C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, $-NHCOCH_3$, $-NH(C_1$ - C_2 alkyl), $-N(C_1$ - C_2 alkyl) $_2$, $-COO(C_1$ - C_4 alkyl), $-CO(C_1$ - C_4 alkyl), C_1 - C_3 alkoxy, C_1 - C_3 thioalkyl, fluoro, chloro, cyano and nitro; and

R_5 is phenyl or pyridyl, and R_5 is substituted with from one to three substituents

10 independently selected from fluoro, chloro, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(C_1$ - C_6 alkyl) $O(C_1$ - C_6 alkyl), $-NHCH_3$, $-N(CH_3)_2$, $-COOH$, $-COO(C_1$ - C_4 alkyl), $-CO(C_1$ - C_4 alkyl), $-SO_2NH(C_1$ - C_4 alkyl), $-SO_2N(C_1$ - C_4 alkyl) $(C_1$ - C_2 alkyl), $-SO_2NH_2$, $-NHSO_2(C_1$ - C_4 alkyl), $-S(C_1$ - C_6 alkyl) and $-SO_2(C_1$ - C_6 alkyl), and wherein the C_1 - C_4 alkyl

15 and C_1 - C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

comprising reacting a compound of the formula



X I

wherein R_4 , R_7 and R_{19} are defined as above, with a compound of the formula R_5OH or

30 R_5SH , wherein R_5 is defined as above, in the presence of a base.

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/IB 95/00439

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	C07D487/04	C07D239/52	C07D239/48	C07D239/50	C07D473/34
	C07D213/69	A61K31/44	A61K31/505	C07D213/70	C07D213/74
	C07D405/12				

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO-A-94 13676 (PFIZER ; CHEN YUHPYNG L (US)) 23 June 1994 see the whole document ---	1-14
X	DE-A-31 45 287 (TROPONWERKE GMBH & CO KG) 19 May 1983 see page 4, line 1 - line 5; claim 1 ---	1,13,14
A	US-A-5 063 245 (ABREU MARY E ET AL) 5 November 1991 cited in the application see the whole document ---	1-14

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

6 September 1995

Date of mailing of the international search report

12.09.95

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Bosma, P

INTERNATIONAL SEARCH REPORT

Int. J. Appl. Inv. No
PCT/IB 95/00439

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 72, no. 21, 25 May 1970 Columbus, Ohio, US; abstract no. 110080v, K. FUJIKAWA ET AL. 'Herbicidal activities of phenoxyypyridines' page 275; see CAS RN 28373-83-3, 28215-92-1 AND 28215-94-3 see abstract & AGRICULTURAL AND BIOLOGICAL CHEMISTRY, vol. 34, no. 1, 1970 TOKYO JP, pages 68-79, -----</p>	15

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 95/00439

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 14 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 17 and 18 could not be searched, because not all substituents were defined (Art. 6 - PCT).
Claims not searched: 17 and 18
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 95/00439

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9413676	23-06-94	AU-B-	5666494	04-07-94
		CN-A-	1097758	25-01-95
		FI-A-	935585	18-06-94
		NO-A-	952398	16-06-95
DE-A-3145287	19-05-83	NONE		
US-A-5063245	05-11-91	NONE		